Charles University
Faculty of Pharmacy in Hradec Kralove

DIPLOMA THESIS

Exercise as Medicine
Growth Hormone Response to High-intensity Interval Training

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Hradec Kralove 2018 Michaela Bažantová

Declaration

I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing this thesis are listed in the bibliography and properly cited.

In Hradec Kralove:

Aknowlegments

Firstly, I would like to thank my thesis supervisor prof. Marco Bernardi of the Department of physiology and pharmacology at the Sapienza University in Rome. He introduced me into the issue and provided to me with a lot of experience. I would also like to thank Pietro Giacomo Curatulo, who was my biggest support and whose help made this thesis successul. Last, but not least, I would like to thank my Czech thesis supervisor prof. Petr Nachtigal, Ph.D. for his patience and help with finishing my thesis.

Abstrakt

Současný výzkum zaměřený na vyplavování růstového hormonu v souvislosti se cvičením je součástí širšího tématu souvisejícího s pozitivním účinkem vysoko intenzivního intervalového tréninku na zdraví, a proto také patří k tématu “cvičení jako lék”. Víme, že v několika systémech našeho organismu (jako je kardiovaskulární systém, kosterní systém atd.) je náš genom maladaptován. To ukázal již Booth *et al*. ve svých výzkumech. Na vině je pokles fyzické aktivity dnešní společnosti ve srovnání s našimi předky. Proto I reakce růstového hormonu na cvičení je snížena. Je několik mechanismů, jako je zvýšená koncentrace laktátu v krvi, zvýšená koncentrace vodíkových iontů v krvi, afferentní signály ze svalových vláken, které jsou považovány za hlavní podněty pro vyplavení růstového hormonu vyvolaného cvičením. Cílem tohoto výzkumu je studium možného metabolického podnětu relativní svalové hypoxie, což je poměr mezi poptávkou po energii a dostupností kyslíku, jako hlavního regulátoru produkce růstového hormonu.

Abstract

The present research focused on growth hormone response to exercise is part of a wider project related to the beneficial effect of high-intensity interval training and therefore is related to the topic of “exercise as medicine”. We hypothesized that as shown by Booth *et al*, in several systems of our organism (such as the cardiovascular system, skeletal system etc.) our genome is maladapted, because of our reduced physical activity compared to our ancestors. Therefore, also the growth hormone response (GH) to exercise is decreased. Several mechanisms, such as increased lactate concentration in blood, increased hydrogen ion concentration in the blood, afferent signals from muscle metabolic receptors etc., have been proposed as stimuli for the GH response to exercise. The aim of the present research is the study of a possible metabolic stimulus of a relative muscular hypoxia, which is the ratio between energy demand and oxygen availability, as the main regulator of the growth hormone production.

Index

1. INTRODUCTION

This diploma thesis is concerned with the exercised induced effect of growth hormone to humans' health. Growth hormone constitutes an important factor not only for muscle growth and regeneration, but its effect on body composition, in terms of fat mass reduction, is also suggested. Reducing or maintaining the required level of fat mass is an important prerequisite for health. It is suggested that physical activity is important for our health and should be an integral part of every individual's life, regardless of age or gender. Unfortunately, nowadays, exercise has disappeared from everyday life and this causes a lot of complications. Weight gain and obesity are some of the biggest issues. In programmes for fat mass reduction, the long-lasting and low-intensity aerobic exercise is considered to be the most effective. We compare the effectiveness of aerobic exercise with anaerobic work. High-intensity interval training, during which the growth hormone levels are higher, provides greater burning efficiency and hence weight reduction, especially the reduction of fat tissue. The advantage is an increase in muscle mass and other benefits which are associated with this effect.

2. THEORETICAL PART

2.1 Exercise and gene expression: physiological regulation of the human genome through physical activity

Our genome has been modulated for a very long time and it was selected in a time frame when physical activity was needed for survival because of the hunting and gathering behaviour of our Late Paleolithic ancestors. It has been suggested that human evolution has been selected for genes which are promoted by physical activity. Despite the fact that just a few generations ago, physical activity was considered to be an integral part of human's life, physical inactivity actually seems to be part of the normal lifestyle now. Sedentary lifestyle, which is nowadays typical in western countries, would in those days cause the elimination of individuals because they would not have been able to gather the resources in order to survive. Unfortunately, physical inactivity is an epidemic which affects everyone in every nation, even though the effects of a declining physical activity level can be observed more acutely in countries where economies are rapidly developing (Eaton *et al*., 2002).

Our phenotype has changed a lot in the last thousands of years, but the current genotype could not keep up with the pace of lifestyle, resulting in maladaptation. It has not had the opportunity to adapt to the new environment, thus it produces an abnormal gene expression. These are the bases on which some diseases occur. There is not only the problem of rising rates of chronic disease, but also the actual life expectancy is shortened, and health care costs are escalating (Booth *et al*., 2002).

From this perspective, it seems reasonable to think that some level of physical activity is required for a normal expression of the genes of our genome. It is the reason why sedentary lifestyle causes perturbations in homeostatic mechanisms. We can deduce that some gene functions were developed in accordance with the need for exercise. Physical inactivity is linked to a loss of function which results from silencing of genes. However, the problem is not a genetic defect of the gene but the environmental interaction and the lack of physical activity with the expression of the gene (Pérruse&Bouchard *et al.*, 1999).

We can also say that physically active individuals use more energy than sedentary ones, even when they are not moving. Their basal metabolism is higher. Ron Evans engineered transgenic mice, to overexpress the gene called peroxisome proliferator-activated receptor delta (PPARδ). This gene causes an increase in the number of mitochondria in skeletal muscle. It converts some muscle fibers to a slow-oxidative phenotype, which is the type developed by aerobic physical activity, and it protects the organism against the development of obesity. These transgenic mice burned more calories, even with a high-fat diet, than the mice without the extra protein encoded by PPARδ (Booth *et al*., 2005).

To say that our genome is modulated according to the level of physical requirements for survival and the lifestyle of humans in those ancient times, we can compare lifestyles than and now. Physical activity nowadays is different from the amount of physical activity in the Late Paleolithic. For example, the daily expenditure declined from 206 kJ/kg/day to 134 kJ/kg/day. This is the result of the changes we brought to our environment in order to spare ourselves the need for physical activity for survival means. It is assumed that a typical hunter-gatherer H. Sapiens expended about 4.185 kJ on an average every day involved in physical activity and their calorie intake was about 12.555 kJ. The ratio 3:1 is called substance efficiency. A typical sedentary person uses 1.255 kJ by physical activity, which provides a ratio 8:1. Therefore even if today's caloric intake is reduced, people do not burn enough calories through physical activity and there is an excess of 418,5 kJ per day. This fact results in weight gain and rising morbidity and mortality risk (Cordain *et al*., 1998).

As previous mentioned, there is a big difference between the habits of the current humans' lifestyle and the harsh conditions under which human biology evolved. The fact that our skeletal muscles are underused is the reason why many physical illnesses occur, and it also plays a major role in the rise of chronic diseases. We can also look at the amount of human muscle mass. People in the Late Paleolithic era had larger muscle mass than humans today.

If we take today's Olympic athletes as a specimen of extraordinary fitness for our standards, we have to consider that our ancestors from the Paleolithic era were almost as fit on average (Booth *et al*., 2005). Nowadays, machines and technological innovations relieve human beings from hard physical work while there used to be times when work was required for survival. The lack of physical exercise is a byproduct of innovation and economic progress which we can see rise rapidly in more developed countries. It can be said that as economies grow, people tend to stop practising physical exercise. In the United States, as one of the most developed countries, the level of physical activity has been reduced by as much as 32 percent in just two generations (Council of Europe, Charter of Sport: Strasbourg, 1992).

The effects of physical inactivity start very early, and consequences experienced over an individual's lifetime are dramatic. It is a deadly cycle which begins with the fact that today's children are dropping out of sport and physically active play at a very young age. Seventy-five percent of American children dropped from practicing physical activity between the age of 9 and 15 (Nader *et al*., 2008). In Europe, this number lies around 50 percent, which is however alarming (Riddoch *et al*., 2004). This phenomenon of physically inactive children predicts consequences in the population such as higher obesity risk, more missed school days, lower test scores, lower income (Stevenson B., 2010), higher health costs (Cawley *et al*., 2012)., more sick days (Proper *et al*., 2005) and higher probability of obesity in adulthood (Lee *et al*., 2012).

The question is how it is possible to deceive the body to think that we have gone through enough physical activity even if we have not got the time to practise it all the day long as our ancestors did (Booth *et al.*, 2007).

2.2 Social costs and economic consequences

Physical inactivity can be considered a major risk factor for all-cause mortality and it contributes to worsening most diseases (U.S. Department of Health and Human Services, 2008). This brings higher need of health care and, of course, more money to the budget of the Department of Health in every country. The price of inactivity was measured in a new research and we can look to the future and get to know its consequences (Hallal *et al*.,2012).

It has been determined that in 2008 the cost of treatments for the diseases directly associated with physical inactivity in China, India, the U.K. and the U.S. was more than 200 billion U.S. dollars (Hallal *et al*., 2012).

If we look at how much do the direct and indirect effects associated with inactivity cost and we assume the same trend continues up to 2030, we can see that the growth of the figures of healthcare budget will grow by 113% in the U.S., while in India by 447% (U.S. Department of Health and Human Services, 2001).

Sedentary lifestyle is expanding in Europe (in Italy it involves 64% of adults and 57% of the infant population - ITALY PAFS 2016), generating a total expenditure of 80.4 billion euros a year within the Union and of 12.1 billion euros in Italy (International Sports and Culture Association, 2015). The cost of health care for an obese people is about 25% higher than for those who have not got a high body mass index (Withrow *et al*., 2010), and according to the forecast, an obese eighty-year-old's social cost will be about 100 thousand euros higher than the one that can be estimated for a normal-sized person.

This was the global point of view, however, we can take into account the fact that inactive individuals have lower income, are less productive in their job, take more extra sick days in a year and are not as successful in their jobs as physically active people. All these factors confirm the outflow which inactive people cause to the economy.

2.3 Benefits and risks of regular physical activity and/or exercise

2.3.1 Terminology

Before we think about the benefits and risks of the physical activity, the main terminology needs to be explained. First, we need to know what physical activity is. We can describe it as any bodily movement which is produced by the contraction of skeletal muscles. Another term, which will be used, is exercise. It can be said that it is a planned, structured and repetitive physical activity leading to an improvement of physical fitness. The word "fitness" expresses a set of attributes which are needed for practising physical activity. We can mention maximal aerobic strength, anaerobic capacity, body composition, and flexibility. Also, it is important to define the wide range of exercise intensities which are associated with physical activity. We can use several methods to point out benefits and limitations: percentages of maximal oxygen consumption (VO_2max), oxygen consumption reserve (VO_2R), heart rate reserve (HRR), maximal heart rate (HR_{max}) or metabolic equivalents (METs) appear to be the most useful methods. The level of intensity depends also on the type of exercise performed. In an aerobic exercise, the level of intensity is assessed through the evaluation of the percentage of maximal oxygen uptake or better through a percentage of oxygen uptake reserve (Caspersen *et al*., 1985). A generally useful tool to describe intensity is granted by METs, which means metabolic equivalents, corresponding to a multiple of the metabolic expenditure tested at rest (approximated by convention to 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$). Light activity is defined as <3 METs, moderate activity requires 3-6 METs and vigorous activity >6 METs. Almost every kind of physical activity has been measured and data about different types of usual activities with METs consumption are available. Unfortunately, many measures are not taken into account. These are for example age, BMI and other differences between individuals (it is known, in fact, that even if they work in the same range of MET, individuals of different age experiment relative exercise activities, defined by VO_2max, which can be diametrically different). It is suggested to match the intensity defined by METs to the fitness level of each individual (Haskell *et al*., 2007).

2.3.2 Benefits

It is well known that physical activity provides health benefits, which means that it underpins physiological adaptation. It decreases resting blood pressure, thus reducing the risk of developing diseases (e.g. cardiovascular diseases) (Kraemer W. *et al*., 2016h).

There are not only health benefits of a physical activity but also fitness benefits, such as increased lactate threshold, vertical jump ability, improved agility, coordination, balance, power, reaction time, speed and maximal strength. Some physical adaptation can bring both fitness and health benefits, such as the increased peak of oxygen consumption, which can increase performance in endurance sports and also represents also a strong predictor of overall mortality (Kesaniemi *et al*., 2001).

2.3.3 Recommendation

Studies were carried out to clarify the amount and intensities of physical activity needed to improve health, lower morbidity and decrease mortality. Those documented the dose-response relationship between health and physical activity 54. It is clear that any additional amount of physical activity provides further health benefits and there is also and inverse dose-response relationship between physical activity and mortality, overweight, obesity and fat distribution, DM2, colon cancer, depression and anxiety, osteoarthrosis and general quality of life (Kesaniemi *et al*., 2001). The result provides the following recommendations which should ideally reform public health. We can define five important points:

- Healthy adults (aged 18-65) need moderate-intensity physical activity for a minimum of 30 minutes five days per week, or vigorous activity for a minimum of 20 minutes three days per week;
- Point one can be combined;
- Moderate-intensity aerobic activity can be accumulated reaching the 30-minutes threshold by performing bouts of the duration of 10 or more minutes each;
- Everyone should perform activities to increase muscular strength and endurance at least twice a week;
- Individuals who wish to further improve their personal fitness should safely exceed the minimum recommended amounts of physical activity; (Haskell WL., 1978).

There is a lot of evidence and studies which were carried out to support the relationship between regular physical activity or/and exercise and premature mortality, coronary artery disease, cardiovascular disease, hypertension, stroke, osteoporosis, DM2, metabolic syndrome, obesity etc. (Feskanich *et al*.,2002; Haskell *et al*., 1978; Kesaniemi *et al*., 2001; Leitzmann *et al*., 1999). In general, it can be said that it improves cardiovascular and respiratory functions via increasing the maximal oxygen uptake, decreasing the ventilation per minute, decreasing myocardial oxygen demand for a given absolute submaximal intensity, decreasing the heart rate and blood pressure, increasing capillary density in skeletal muscle and increasing exercise threshold for the accumulation of lactate in the blood. It reduces risks factors of coronary artery disease through reducing resting systolic/diastolic pressure, increasing serum HDL and decreasing TGL, reducing total body fat and also intra--abdominal fat, reducing insulin needs and improving glucose tolerance, reducing blood platelet adhesiveness and aggregation. It decreases morbidity and mortality and plays a role in both primary and secondary prevention (primary prevention means that initial occurrence of a disease is avoided, while secondary prevention is needed to prevent another similar event after the first from happening). Moreover, it has a positive influence on decreasing anxiety and depression, it enhances physical functions and feelings of well-being, it also reduces the risk of falls and injuries and provides an effective therapy for many chronic diseases, especially in older adults (Atterhog *et al*., 1979; Kesaniemi *et al*., 2001; Manson *et al*., 2002).

2.3.4 Risks

It must be said that the benefits largely outweigh the risks, but we must mention the risk of occurrence of sudden cardiac arrest or myocardial infarction, which can occur in individuals performing exercise at vigorous intensity, more likely in individuals who present some risk factors (e.g. atherosclerosis or hypertension). It is clear that the most common causes of death in young individuals are congenital and hereditary abnormalities which include hypertrophic cardiomyopathy, coronary artery abnormalities, and aortic stenosis. The risk of sudden cardiac events is higher in adults than in younger individuals because of higher prevalence of cardiovascular disease in the older population. The absolute risk of sudden cardiac death during vigorous activity is one per year for every 15.000-18.000 people (Siscovick *et al*., 1984;

Thompson *et al*., 1979). The rates of sudden cardiac death and acute myocardial infarction are higher in the sedentary individuals when they perform an unaccustomed exercise which is infrequent. Now it is clear that the highest risk of cardiovascular events occurs in those individuals who suffer from any coronary artery disease. It is very difficult to test the effectiveness of strategies for reducing the occurrence of the cardiac events because of the low prevalence of these events related to vigorous exercise (American College of Sports Medicine positions stand, 1998). In general, exercise does not provoke cardiovascular events in individuals with a normal cardiovascular system, but even though the benefits of physical activity outweigh the risks, physicians should not underestimate the risks. There are some recommendations for physicians and for any individuals who want to engage in physical activity:

- Healthcare professionals should know how to appropriately evaluate physically active children and adults, bearing in mind the pathologic conditions associated with exercise-related events.
- Active individuals should know how the cardiac prodromal symptoms show.
- Active individuals, especially high school athletes, should be screened by qualified professionals.
- Individuals with known cardiac conditions should be evaluated for competition using published guidelines.
- Staff in healthcare facilities should be trained in managing cardiac emergencies and have a specified plan and appropriate resuscitation equipment.
- Active individuals should modify their exercise program according to variations in their exercise capacity, habitual activity level and the environment (American College of Sports Medicine positions stand, 1998).

All strategies for reducing the number of cardiovascular events say that sedentary individuals should begin with light- to moderate-intensity physical activity programs and exercise at a lower rate to avoid or minimalize the risk of sudden cardiac events. Everyone should be educated on the signs and symptoms of cardiovascular disease and should be under control of healthcare professional if symptoms occur (American College of Sports Medicine positions stand, 1998).

2.4 Components of physical fitness related to health

2.4.1 Body composition

One of the most popular benefits of physical activity is improving of body composition, which is a physical fitness component. The goal of improving body composition is typically increasing muscle mass and decreasing body fat, which brings health benefits, improves body image and also increases physical performance. Body mass and body composition is not reliant on exercise regime, but it is also closely linked to diet and nutrition (Kraemer *et al*., 2016a).

Body composition is mostly divided into the absolute amount of fat and non--fat tissue to determine the ratio of the total body mass (TBM). Fat mass (FM) is the total amount of fat in the body, whereas fat-free mass (FFM) is the total mass of body excluding fat. Another term which is used for fat-free mass is total lean tissue. This term is used in one of the new techniques of determining body composition called DEXA (dual-energy x-ray absorptiometry). If we know the total fat mass and total body mass, we are able to count the percentage of body fat (% fat) (Kraemer *et al*., 2016a).

Another useful number is the body mass index (BMI) which, with other statements, can help in recognizing overweight and obesity. It is the ratio of body mass divided by height. It can be calculated by the following equations:

BMI (kg/m^2) = weight (kg) or weight (lb) x 703 height (m^2) height (in^2)

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{weight (kg)}}{height\ (m^2)}$$

Normal levels of BMI are between 18.6 and 24.9. Higher BMI indicates overweight or obesity, whereas lower shows underweight. The population can be divided into 6 groups according to the BMI value. The next figure shows BMI classifications.

Figure 1 Classification of body status according to BMI

Classification	BMI (Kg/m^2)
Underweight	<18,5
Normal	18,5-24,9
Overweight	25,0-29,9
Obesity class I	30,0-34,9
Obesity class II	35,0-39,9
Obesity class III	>40,0

(National Institute of Health, 1998)

Following figure shows BMI prediction and percentage body fat with the level of health risk.

Figure 2 Risks releated to BMI level

BMI(Kg/m2)	Health risk	20-39 years	40-59 years	60-79 years
Men				
<18,5	Elevated	<8,5%	<11%	<13%
18,5-24,9	Average	8%-19%	11%-21%	13%-24%
25,0-29,9	Elevated	20%-24%	22%-27%	25%-29%
>30,0	High	>25%	>28%	>30%
Women				
<18,5	Elevated	<21%	<23%	<24%
18,5-24,9	Average	21%-32%	23%-33%	24%-35%
25,0-29,9	Elevated	33%-38%	34%-39%	36%-41%
>30,0	High	>39%	>40%	>42%

(Whaley *et al*., 2006)

Even though the BMI is a helpful tool for health risk indication, it does not take into account body composition directly. It can happen, for example, that an athlete has a BMI indicating overweight, while their body fat is very low. In the athlete's body, there are a lot of muscles which are very heavy and that is the reason why the BMI can provide high value. It is irrelevant to determine body composition in lean, muscular athletes (Ode *et al*., 2007).

As it is well known, overweight and obesity are associated with increased mortality and also morbidity. Obesity is a primary factor for developing of hypertension and cardiovascular disease in general, type 2 diabetes, arthritis or menstrual abnormalities and complications during pregnancy. It also has a negative effect on the blood lipid profile, can cause sleep apnea and can worsen the risk of some types of cancer such as uterine or colorectal (Calle *et al*., 2003; Fontain *et al*., 2003; Katzmarzyk *et al*., 2005; Pi--Sunyer *et al*., 2002).

If we know how much of fat mass an individual has, it is important to detect the distribution of fat. Central obesity also termed android obesity means that fat deposition is in the abdominal area. This type of obesity is more dangerous than peripheral obesity, also termed gynoid type obesity, which means that fat deposition is in the gluteal and thight regions. The reason, why belly fat is more dangerous is because its stored triglycerides are more likely to release free fatty acids into the blood stream. That is why it is so important to locate the fat tissue in the body (Wong *et al*., 2004).

Other two terms which should be separated are body composition and body size. It is possible to find two individuals with the same size but different body composition, such as the percentage of fat. Anthropometry can help with this problem; it is the measurement and study of body size providing data about body circumferences, bone, breadths and limb lengths (Kraemer *et a*l., 2016a).

2.4.2 Cardiovascular system

It has been suggested that regular physical exercise positively influences the cardiovascular system, whereas cardiorespiratory fitness is considered to be a strong predictor of cardiovascular disease and all-cause mortality (Kodama *et al*., 2009). Increasing cardiorespiratory fitness means decreasing cardiovascular disease risk (Lee DC *et al*., 2011). The range of effects on the cardiovascular system depends up the frequency, duration, and intensity of the exercise. It has been shown that a long period of regular intensive exercise, such as more than 6 months, can decrease heart rate by about 5-20 beats in previously untrained participants. Also, an increase in stroke volume was observed. All four chambers increase in volume, the wall becomes thicker and it results in greater cardiac mass. In literature, the term “athlete’s heart” is used for summarizing all adaptations which affects the structure, electrical conduction and function of the heart which causes an increase in cardiac output during exercise (Swedish National Institute of Public Health, 2010).

It is also suggested that even though aging is linked to changes to the cardiovascular system, such as reduction in functional capacity, regular exercise training can slow this negative progress (Wilson *et al.*, 2011).

In general, the growth of the heart can be physiological or pathological. In the case of exercise-induced growth, it is a physiological process. This is associated with a normal cardiac structure, no cell death, no fibrosis, cell hypertrophy and improved cardiac function (Waring *et al.*,2014). On the other hand, pathological remodelling is associated with the death of cardiomyocytes, cardiac dysfunction or an increased risk of sudden death caused by heart failure (Weeks *et al.*, 2011).

Exercise training affects also endothelium, which is a single layer of the cells and plays a big role in the vascular adaptations to exercise. Endothelium can produce vasoactive hormones that change the tone of resistance and conduit vessels. However, nitric oxide (NO) is the main substance. It can, through its antithrombotic and antiatherogenic functions, cause relaxation and vasodilatation of muscle cell. NO is released in response to and increase in the flow of blood. If this is repeated, it provokes vascular adaptation and artery remodelling (Green *et al.*, 2008).

In response to exercise, both functional and structural changes occur. How big the changes are depending on the individual’s health and fitness status and also on the intensity of exercise. There is no doubt that the phenotype of an athlete's artery is different from that of sedentary individuals'. There is a larger lumen with a thinner wall. (Hollis *et al*., 2012).

It seems that high-intensity interval training is the best training program for improving cardiovascular health and cardiorespiratory fitness. Significantly greater increase in VO_2max which represents aerobic capacity has been observed across a broad range of populations. Even for healthy sedentary people and patients with heart failure is HIIT program more effective than exercising at moderate intensities. VO_2max is considered to be a valuable marker of cardiovascular disease more than any other risk factor. Regular, intensive and sustained exercise is demonstrably the most advantageous for optimizing cardiovascular health (Weston *et al*., 2014).

2.5 Exercise prescription

2.5.1 Aerobic training guidelines

Aerobic training guidelines have been developed for improving aerobic capability in people who want to improve their fitness and health and have little or no experience with performing endurance exercise. There is a difference in exercise prescription for health-related or skill-related goal. Despite the goal being an improvement of individual's fitness status, health benefits, such as protection from cardiovascular disease, osteoporosis or cancers, occur. There are some suggestions including duration and intensity of exercise, however, these are highly individual, and they vary from person to person. Some people may improve their aerobic fitness by exercising less than it is suggested and, on the other hand, some people need to increase the amount and intensity of exercising. There are guidelines prescribed by the American College od Sports Medicine and the American Heart Association, which should decrease the risk of chronic disease, but they are not appropriate for most competitive or recreational athletes with a high level of aerobic fitness. For these athletes is necessary to create more advanced program. The prescription of aerobic training exercise consists of four basic components which are type of exercise, duration of each exercise session, frequency of training and intensity of exercise (American College of Sports Medicine., 2013).

2.5.1.1 Type

Aerobic exercise usually involves several large muscle groups. Mostly prescribed are jogging, running, cycling, spinning, swimming, rowing or aerobic dance and it depends on each individual what he or she prefers. The most important is that it should be enjoyable which is a prerequisite maintaining the target and if a person enjoys the exercise, they are more likely to exercise for their entire life. Naturally, what must be taken into account is the ambitiousness of the exercise and individuals' availability to perform an activity. What is very helpful is to change the activity sometimes, to break the stereotype and avoid the loss of motivation or minimize the chance of injuries. This change is called "cross-training" (American College of Sports Medicine, 2013).

2.5.1.2 Duration of training

For most adults, the recommendation is a longer session of 30 to 60 minutes of moderate intensity. Even if 30 minutes of moderate exercise provides similar results to 10 minutes of vigorous exercise, it is recommended to perform the longer-lasting moderate activity because high--intensity exercise is associated with greater chance of injury and lower adherence to training (Kavouras *et al*., 2007).

2.5.1.3 Frequency of training

The frequency of training is closely related to training intensity. However, the optimal frequency is 3 to 5 days per week. Grater frequencies may be possible if the type of activity is changed or if a combination of moderate- and vigorous-intensity exercise is used. The additional training sessions may be beneficial in case that the trainer's goal is to decrease body fat (American College of Sports Medicine, 2013).

2.5.1.4 Intensity of exercise

The most practical way to determine exercise intensity is the percentage of maximal heart rate (HR_{max}). Moderate intensity corresponds to 40-60 % of heart rate reserve. However, there are individual variations in the minimal intensity which is needed to achieve the target depending on training goals and initial fitness level. As it is obvious, trained athletes need to use higher intensities than healthy adults to attain aerobic fitness gains. The same still applies, there is a range of intensities corresponding to the training goal and initial fitness level. Also, there are many methods to determine the right intensity (American College of Sports Medicine, 2013).

2.1.1.1.1 Exercise heart rate

Exercise heart rate (HR) is the most used tool to determine the intensity of exercise. There is a linear relationship between increasing workload and oxygen consumption. At maximal oxygen consumption, there is HR plateauing. Thanks to this relationship, HR is measured and used to determine the intensity of exercise. The best way of finding out the individual's accurate HR_{max}, is to measure it during an exercise stress test. This measurement provides the greatest accuracy however, it is not possible to use it in every case. Thus, there are other possibilities to estimate HR_{max}, for example by calculating through a common equation (Kraemer *et al.*,2016b):

$$HR_{max} = 220 - \text{age in years}$$

Unfortunately, there are some errors in estimating HR_{max}, so more appropriate equation was estimated as follows

$$HR_{max} = 207 - (0.7 * \text{age in years})$$

To show one example, we can use a 25-year-old individual. We will estimate HR_{max} and moderate-intensity HR range, which is needed to achieve the aerobic fitness benefit:

$$HR_{max} = 207 - (0.7 * 25)$$

$$HR_{max} = 189{,}5 \text{ beats per minute (bpm)}$$

$$64\% \text{ of } HR_{max} = 189{,}5 * 0{,}64 = 121{,}5 \text{ bmp}$$

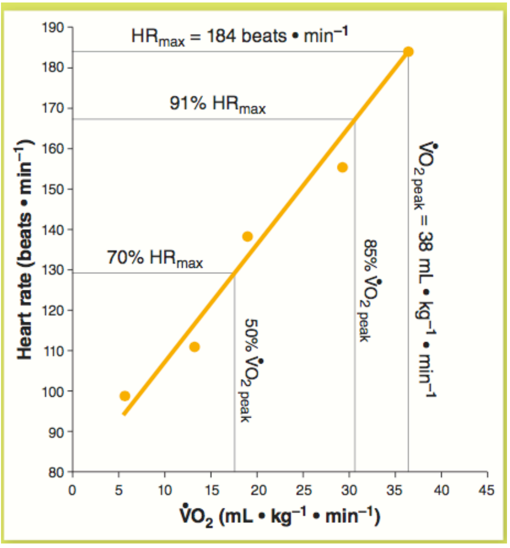
$$76\% \text{ of } HR_{max} = 189{,}5 * 0{,}76 = 140{,}2 \text{ bmp}$$

From this equation we got an accurate HR range for aerobic exercise for an individual of the age of 25. Aerobic training zone is 121,5 bpm to 140,2 bpm (Kraemer *et al*., 2016b).

- Heart rate reserve method

This method is a useful tool used to estimate the HR needed to exercise at a specific percentage of peak oxygen consumption. In the Figure 3, we can see the relationship between the percentage of peak oxygen consumption and heart rate. 91% of HR_{max} is equivalent to 85% of peak oxygen consumption and 70% of HR_{max} is equivalent to 50% of peak oxygen consumption (American College of Sports Medicine., 2010).

Figure 3 Heart rate reserve method



(Adapted from ACSM's 8th ed., 2010)

Moderate aerobic exercise is defined as a 40-60 % of heart rate reserve (HRR) and the vigorous one as a 60-90% of HRR. HRR method differentiates resting heart rate (HR_{rest}) and maximal heart rate (HR_{max}). Target HR (THR) is the HR, which should be performed at a certain percentage of peak oxygen consumption. There is an equation which can estimate the THR at any percentage of peak oxygen consumption. The given example estimates the THR needed for exercise at 60% of peak oxygen consumption (American College of Sports Medicine, 2013):

$$HRR = HR_{max} – HR_{rest}$$

$$HRR = 190 \text{ bpm} – 75 \text{ bpm}$$

$$HRR = 115$$

$$\text{THR at 60\% of peak oxygen consumption} = HR_{rest} + 0.60\ (HRR)$$
$$= 75\ \text{bpm} + 0.60\ (115)$$
$$= 144\ \text{bpm}$$

This calculation estimates that a THR of approximately 144 bmp would result in exercising at 60% of peak oxygen consumption. With an increasing level of aerobic fitness status, an individual is able to perform more work (such as run or cycle faster) at any given HR. With improvement of aerobic conditions, HR at any given workload tends to decrease. Also, HR at rest can decrease slightly. This phenomenon can show the progress of an individual. In any case, training should be progressed slowly to minimize the risk of injury, fatigue or overtraining. Some periods with a lower difficulty of training than the previous session can be placed in the training session to decrease the chance of injury or detraining, and it allows for recovery. This period is quite short and will not cause loss of fitness gains (Kraemer *et al.*, 2016b).

2.5.2 Resistance training guidelines

Similarly to guidelines for aerobic training, resistance or weight training guidelines have been developed as well. They are intended for novices, but also for advanced sportspeople with a long history of resistance training experience (American College of Sports Medicine, 2009). These guidelines should bring both health and fitness benefits. Resistance training contains several basic components, such as the type of exercise, the volume of one session, the length of rest period between sets, the frequency of training and intensity od exercise. Resistance training provides an increase in maximal strength or muscle hypertrophy (American College of Sports Medicine, 2009).

2.5.2.1 Type

There is a wide range of equipment, which can bring about increase in maximal strength or muscle hypertrophy. The most frequent are barbells, dumbbells, rubber cord, body weight and resistance training machines. Each programme typically includes at least one exercise focused on each major muscle group of the body. We differentiate multi-muscle group exercises and single-muscle group exercises. The first group of exercises involves movement at more than one joint and force is developed by more than one muscle group. The second group of exercises involves movement at one joint and force is developed by one muscle group. The base of a session should contain multi-muscle group exercises, which are placed at the beginning of a training session, whereas single-muscle group exercises are considered to be assistance exercises. Resistance training programme should contain both agonist and antagonist (low back and abdominal muscles), to avoid muscle imbalances (American College of Sports Medicine, 2009).

2.5.2.2 Volume of one session

The volume of an exercise session is dependent on an individual's fitness level. In prescription is determined a number of exercises, number of sets and number of repetition per set. Usually, training volume is changing to maximise strength, hypertrophy, local muscular endurance or power. Single--set training is appropriate for beginners, however, over time, the volume of training should increase. For those, who are accustomed to training, higher training levels are necessary to elicit their maximal gains. For muscular strength improvement, 8 to 12 repetitions per set are recommended. The resistance of each repetition is approximately 60% to 80% of the one repetition maximum resistance. The number of repetition depends on the goal of the training programme. Higher numbers of repetitions emphasize endurance, whereas lower numbers emphasize strength and maximal power (Rhea et al. 2002). In the next figure, there are examples of training with respect to the athlete's target.

Figure 4 Types of training

Frequency per Week	Number of Sets per Exercise	Number of Repetitions per Set	Intensity Percentage of 1-RM	Rest Between Sets
Emphasize Maximal Strength				
Novice trainer				
2–3 total body sessions	1–3	8–12	60–70%	2–3 min major exercises 1–2 min assistance exercises
Intermediate trainer				
3 total body sessions and 4 split routines	Multiple	8–12	60–70%	2–3 min major exercises 1–2 min assistance exercises
Advanced trainer				
4–6 split routines	Multiple	1–12	Up to 80%–100% in a periodized manner	2–3 min major exercises 1–2 min assistance exercises
Emphasize Hypertrophy				
Novice trainer				
2–3 total body sessions	1–3	8–12	70–85%	1–2 min
Intermediate trainer				
3 total body sessions and 4 split routines	1–3	8–12	70–85%	1–2 min
Advanced trainer				
4–6 split routines	3–6	1–12 (mostly 6–12)	70–100% in a periodized manner	2–3 min major exercises 1–2 min assistance exercises
Emphasize Power				
Novice trainer				
2–3 total body sessions	Maximal strength training + 1–3 power-type exercises	3–6 (not to failure)	Upper body: 30–60% Lower body: 0–60%	2–3 min for major exercises with high intensity 1–2 min assistance and major exercises with low intensity
Intermediate trainer				
3–4 total body or split routines	Novice + progression to 3–6 power-type exercises	Novice + progression to 1–6	Novice + progression to 85–100%	2–3 min for major exercises with high intensity 1–2 min assistance and major exercises with low intensity
Advanced trainer				
4–5 total body or split routines	novice + progression to 3–6 power-type exercises	Novice + progression to 1–6	Novice + progression to 85–100%	2–3 min for major exercises with high intensity 1–2 min assistance and major exercises with low intensity
Emphasize Local Muscular Endurance				
Novice trainer				
2–3 total body sessions	Multiple	10–15	Low	1 min or less
Intermediate trainer				
3 total body sessions and 4 split routines	Multiple	10–15	Low	1 min or less
Advanced trainer				
4–6 split routines	Multiple	10–25	Various percentages	1 min or less 10–15 reps 1–2 min 15–25 reps

(Adapted from Ratamess *et al.*, 2009)

2.5.2.3 Length of the rest period between sets and exercise

The shorter the rest period, the lower chance for recovery of the anaerobic energy stores (such as ATP and phosphocreatine) and the more time used to decrease blood and muscle acidity. Short rest results in greater fatigue but in acute hormonal responses, such as increased GH level. This consequence is important for long-term muscle hypertrophy. Longer rest periods (such as 2-3 minutes) are used for maximizing strength and power, whereas short rest (1-2 minutes) is used for increasing in local muscular endurance and hypertrophy (Kraemer *et al*., 2016c).

2.5.2.4 Frequency

It is usual to train three or four times per week. During each training session, all major muscle groups should be trained if it is a total body resistance training program. But with split routine, the body is divided into areas, which are trained in separate sessions, such as upper body or lower body session. Usually, as individual's fitness level increases, the total number of sessions during a week increases too (American College of Sports Medicine, 2009).

2.5.2.5 Intensity

The intensity of resistance training exercise is determined by a percentage of the maximal weight, which a person is able to lift for one complete repetition of an exercise (1-RM). The lower the percentage of 1-RM, the bigger the number of repetitions possible in a set. Another definition for repetition maximum is a number of repetitions in a set to the point at which no more repetitions are possible. Usually, sets should be performed at least to a point close to failure (Kraemer et al., 2016c).

2.5.3 Interval training

Interval training is a type which is performed by soccer, volleyball or basketball players and consists of a greater amount of intense training with rest periods. This results in a greater fitness gain. It has been suggested that interval training results in increasing in peak oxygen consumption in comparison to performing of moderate exercise which shows no significant increase. Also, increase in left ventricular stroke volume was observed. It is important to note, that both groups (HIIT and moderately trained men) trained 3 times per week for 8 weeks and the total amount of work performed was equal. Nowadays, it is obvious that interval training is suitable even for swimming, running, rowing and also as a general fitness routine.

Each interval training session varies in duration (or distance), intensity, duration or type of rest periods, number of interval repetitions per set, and frequency. How the training session is built up depends on the athlete's target. For examples, if sprint ability is to be improved, then short-duration, high--intensity with long rest periods is performed (Helgerud *et al*., 2007).

2.5.3.1 Training intensity

This statement is usually defined as a percentage of HR_{max}. Sometimes it is better to define intensity as a percentage of the best time for the length, such as 250 m in 35s. 90-100% of the best time or of HR_{max} is used for training sprint ability, to develop the anaerobic glycolytic system. For training to develop aerobic capabilities, intensity at 75-85% of the best time or 70-90% of HR_{max} is used (Karp *et al*., 2000; Meckel *et al*., 2011).

2.5.3.2 Interval duration

For short-term sprint ability, short-duration intervals (such as 5-10s) are used (Karp *et al*., 2000). For longer distances, intermediate sprint ability or to train the anaerobic glycolytic system, 30s to 2-minute-long intervals are used. But it depends on the goal of the session (Tønnessen *et al*., 2011), for example, a 40-meters interval training increases repeated sprint ability and one-time sprint, but a mix of 50-meter and 200--meters intervals will also increase the maximal oxygen consumption (Meckel *et al*., 2011).

2.5.3.3 Number of intervals

This number depends on the number of intervals which are performed in a set, or repetitions per set, and the number of sets. For example, general fitness training for beginners can consist of 5 to 10-second high-intensity intervals repeated five to ten times. As physical fitness of a person increases, the duration of high-intensity interval can increase up to 30 or more seconds repeated six or eight times (Karp JR, 2000).

2.5.3.4 Rest period

The next exercising interval can not start until HR decrease to 140 bpm (for a 20- to 29-year old person), 130 bpm (for a 30- to 40-year old person) 120bpm (for a 40- to 50-year old person), 115 bmp (for a 50- to 60-year old person). An easy way of managing exercise and rest periods is to follow the work-to-rest ratio 1:3 to 1:6 depending on physical fitness status of an individual (Karp JR., 2000; Fox EL., 1979).

2.5.3.5 Type of rest interval

There are two possibilities for spending the rest period. The first one is a passive one and it is used when a very high intensities of exercise are performed. The second possibility, the active recovery (meaning active lower than lactate threshold) is used when exercise intervals last 30 seconds or longer (Karp JR., 2000).

2.6 Endocrine system

Endocrine system is one of the two major systems which influence physiological responses and adaptations in the body by sending signals or messages. Endocrine system works thanks to substances called hormones. These substances are released from glands into the blood. Hypothalamus, pituitary gland, thyroid glands, adrenal glands or pancreas belong to major endocrine glands of the body. Each hormone has its own receptor where targets and than can influence tissues. But it can cooperate only with that cells which have the specific receptor for the hormone. Endocrine system can affect a lot of body functions, such as sexual and reproductive processes, tissue growth, protein synthesis, degradation or also mood states. Neuroendocrine system is considered to be a network of glands and substances which control different physiological functions (Kraemer *et al.*, 2016d).

Hormones are synthesized through chemical reactions, stored and released from the storage after receiving a signal to do so. There are three types of releasing. The first is endocrine, which means that hormone is secreted to the blood. Paracrine releasing means that a hormone is released into an area where can interact with other cells. The last, autocrine release involves releasing of a hormone from a cell and stimulation of this same cell by the hormone (Kraemer *et al.*, 2016d).

Each hormone is specified by his half-time. It is the time needed for hormone’s concentration in blood to be reduced to half of its peak value.

Some hormones can bind proteins or other molecules which lengthens this time. Oncce a hormone interacts with a receptor, its structure is changed, and it loses its function (Kraemer *et al*., 2016d).

Some hormones, including growth hormone, insulin and others, may be released in bursts or pulses; this is called pulsatility. It provides bigger effect of hormonal signalling (Kraemer *et al*., 2016d).

Every hormonal secretion must be controlled. This is provided by different feedback systems which can control the amount of hormone which is released by a gland (Kraemer *et al*., 2016d).

Hormone secretion is also influenced by circadian and seasonal factors. Some hormones can be released in the same amount during the whole day and night but releasing of other hormones is dependent on the time of day, daylight or season (Kraemer *et al*., 2016d).

The blood is the most important system which transport hormones to their target cells. The blood can be divided into plasma, leukocytes, platelets and erythrocytes, All these components parts on transport of many substances, such as hormones, oxygen or fats (Kraemer *et al*., 2016d).

Three major groups of hormones are differentiated. Steroids, peptides and amines (modified amino acid hormones). All steroids have the same ring as cholesterol, but each steroid has a different function. For example, testosterone is a typical anabolic hormone which promotes protein synthesis, whereas cortisol is a typical catabolic hormone which promotes protein degradation. Amino acid is the base of peptide hormones. Peptide hormones can be consisted of hundreds of basic amino acids. Amines are detectable thanks to nitrogen which is a characteristic compound of the third type of hormones. Catecholamines, mainly adrenalin and noradrenalin are well known amine hormones which play a very important role in exercise physiology (Kraemer *et al*., 2016d).

In the body, there exist special cascade systems called axes. They represent cooperation between glands in hormone production and control of releasing substances. One of the major axes is hypothalamus-to-pituitary axis. There is a close relationship which results in influencing almost every tissue in the body. Hypothalamus controls pituitary gland by two major hormones which are the releasing hormone and inhibiting hormone (Kraemer *et al*., 2016d).

The part of pituitary gland which is called anterior is responsible for answer of the body to exercise (Kraemer *et al*., 2016d).

2.7 Growth hormone

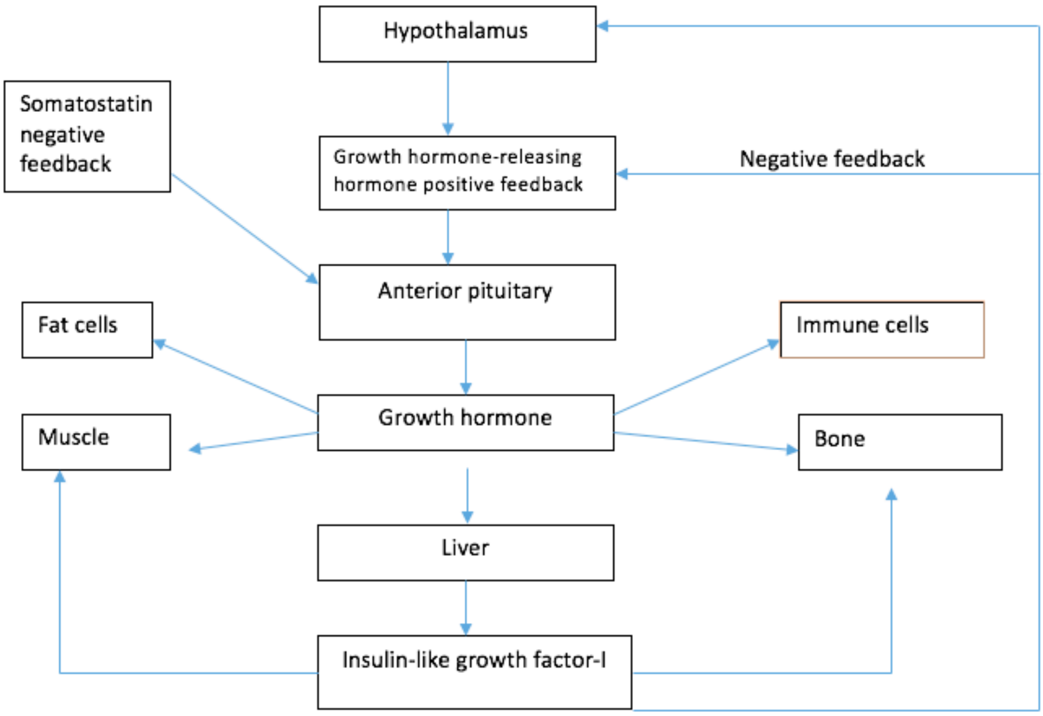
Growth hormone or somatotropin is a polypeptide hormone which stimulates cell division, cellular proliferation, cell regeneration, cell reproduction and growth in general. Cells called somatotrophs synthesize and secrete growth hormone in anterior pituitary gland. It plays different roles in regulation of physiological processes. Growth hormone is an anabolic hormone which means that it can build up tissues. That is a reason why it has been used as a performance-enhancing anabolic drug in sports. Despite the fact that many side effects such as acromegaly or enlargement of flat bones can occur, bodybuilders abuse it because it used to ne non-detectable in a drug test. Growth hormone influences a lot of tissues directly but also indirectly what is realized by interacting with specific receptors of cells (Kraemer *et al*., 2016e).

2.7.1 Functions

Growth hormone has a lot of functions. It can influence anabolism in tissues and organs directly and indirectly as it is shown in the following figure. The direct actions are based on the triglyceride release from adipose tissues. Thus, lipids are not uptaken from the circulation. It also interrupts glucose uptake by the cells to keep relatively normal (healthy) levels of blood sugar. In this way, growth hormone effects can be considered as those of an anti--insulin hormone because of its different anabolic activity with respect to insulin. The indirect effects can be divided into skeletal effects and non-skeletal effects which are both mediated through insulin-like growth factor –I. Insulin-like growth factors IGF-I and IGF-II are major forms of peptides, which were termed somatomedins. The regulation and their function are still not completely well understood due to its complexity. Both are primarily secreted by liver but also by fat cells, or skeletal muscle, and they have anabolic actions for muscle and bone. IGF-I is considered to be a potent regulator of growth hormone release. It is able to facilitate muscle and bone growth, regulate carbohydrate and protein metabolism and takes part during a cell's cycle growth. It is linked and considered to be a biomarker of optimal health and fitness status. Its low level usually predicts negative outcomes in healthy individuals. On the other hand, IGF-II is probably independent of GH control even though it has potent cell reproduction effects and plays role in a fetal growth. The whole family of IGFs is important in exercise physiology, because it takes part in exercise training adaptation and in reparation of bone and skeletal muscle. With physical fitness improving, the resting concentration of IGF-I increases. Acute spikes in its secretion are a result of the intensity and exercise volume, fitness level, and intake of carbohydrate and protein (Kraemer *et al*., 2016e).

The skeletal growth and increasing synthesis of protein are both results of indirect actions of GH. As previously mentioned, growth hormone plays an important role in metabolism of glucose, proteins and lipids; it stimulates the immune system and growth of almost all organs and tissues. For its lipolytic actions and protein synthesis, it is a very attractive substance for sportsmen (Jenkins *et al*., 2001).

Figure 5 Hormonal response



2.7.2 Secretion

In the Figure 5 hormonal response is shown. GH secretion is regulated by hypothalamus. Special cells in hypothalamus release two main peptides which play role in regulation of secretion of growth hormone. Growth hormone--releasing hormone (GHRH) promotes and stimulates releasing of growth hormone and conversely, growth hormone-inhibiting hormone (GHIH) inhibits releasing of growth hormone. There is also a hormone called ghrelin, secreted from the stomach, which can stimulate growth hormone release. Ghrelin binds directly to receptors on the somatotrophs. Growth hormone release reflects on high amounts of IGF in the circulation, which lead to a negative feedback on the hypothalamus and the subsequent release of somatostatin, which inhibits growth hormone release. Physiological processes and factors such as exercise, sleep, nutrition, free fatty acids, age, gender or stress are important effectors of growth hormone secretion (Kraemer *et al*., 2016d).

2.7.2.1 Age

Throughout life, secretion of growth hormone reaches its maximum in teenage years and after that it rapidly falls. Aging also reduces the amount of growth hormone produced during the day and the amount which is released because of acute exercise stress response. There is a big difference between the amount of exercise-induced growth hormone released at the age of 20 and at the age of 60. It dramatically decreases with each decade of aging. This age-releated decreasing .in growth hormone secretion obtains in men more than in women (Pyka *et al*., 1992).

2.7.2.2 Day time

The largest peak occurs an hour after the onset of sleep. That is the main reason why sleep is so important for repair and recovery process. During the day, there are several peaks, mostly induced by exercising. There is no difference in exercise-induced growth hormone release if exercise is performed in the morning or in the afternoon (Galliven *et al*., 1997).

2.7.2.3 Gender

Another difference occurs between genders. It was suggested that women have greater basal secretion, more frequent secretory pulses and their amplitude and even greater mass of growth hormone which is secreted per one pulse than it occurs in men (Pitzzlaf-Roy *et al*., 2002). It was suggested that concentration of growth hormone in young woman is influenced by serum estradiol concentration (Ho *et al*., 1987). When growth hormone releasing was compared between man and woman who were in the follicular phase of cycle, when the level of estradiol is comparable, no gender differences in growth hormone releasing were suggested. Therefore, it is clear that estradiol has a big effect on growth hormone secretion, but the mechanism is not clear. It is obvious that t higher growth hormone release can be obtained only if a woman’s cycle is not changed by contraceptive pills, which maintain the level of estradiol (Müller *et al*., 1999).

2.7.2.4 Body composition

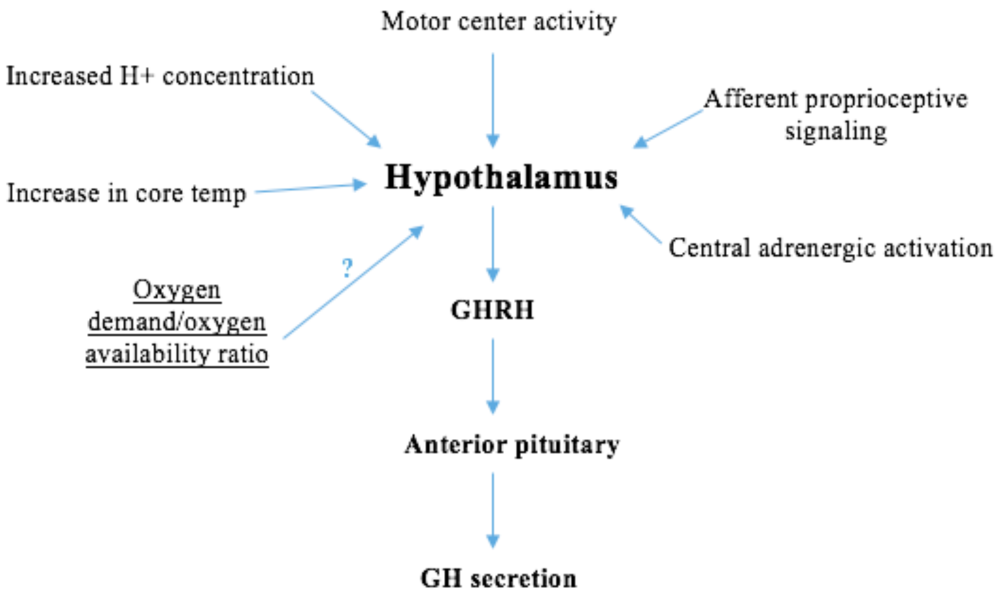
It is known that obesity attenuates growth hormone response (Kanaley JA. *et al*., 1999). Growth hormone concentration is negatively correlated with the percentage of body fat (Veldhuis *et al*., 1995). It has been shown that each unit increase in BMI means reduction in the dialy secretion rate by 6% (Iranmanesh *et al*., 1991). Measuring of abdominal visceral fat, which is considered to be the major determinant od stimulating growth hormone secretion, could be a useful predictor of 24-h growth hormone secretion, of course depending on age and gender of individuals (Vahl *et al*., 1996).

2.7.2.5 Exercise

As previously mentioned, exercise was mentioned to be a potent stimulus for growth hormone release. The amount of growth hormone release depends on the type and intensity of exercise. Actually, even if the amount of growth hormone in circulation increases, protein synthesis is provided only in activated muscle cells. There is a difference of growth hormone release during and after aerobic and anaerobic exercise. Higher levels of growth hormone concentration were obtained during exercise and even in recovery period after anaerobic exercise. (Vanhelder *et al*., 1984). As VO_2peak increases, the GH peak is greater (Pritzlaff *et al*., 1999). If we compare hormonal response to high- and moderate-intensity strength exercise, no differences are obtained. (Raastad *et al*., 2000). However, an interesting point is that resting growth hormone concentration is higher in sedentary individuals than in trained athletes. However, the effect which exercise training has on the growth hormone response to exercise is not clear, and it depends on many factors, which are shown in the next figure (Stokes *et al*., 2000).

2.7.2.6 Mechanism/stimuli regulation GH response to exercise

Figure 6 Mechanism/stimuli GH response to exercise



During and after exercise, different stimuli influence the secretion of growth hormone. In the figure 6, stimuli and mechanisms are shown. Some of them have already been suggested while others are questionable and might be possible topics for new studies. Some potential stimuli for growth hormone release induced by exercise are these (Stokes K., 2003):

- Increased blood lactate concentration

A lot of studies and experiments have been carried out. Thanks to most of them, a correlation between blood lactate and growth hormone concentration was defined, but there were also studies in which different blood lactate accumulation occurred. However, these studies used sodium lactate to artificially manipulate the level of blood lactate and this exogenous form doesn't have any consistent effect on growth hormone concentration. Therefore, we still consider that a mechanism that stimulates anaerobic metabolism can increase blood lactate concentration and also increase the release of growth hormone (Gordon *et al.*, 1994).

- Increased hydrogen ion concentration in the blood

The previous paragraph mentions that blood lactate accumulation is associated with growth hormone release, but it is more likely that it is connected with hydrogen ion (H^+) accumulation. In studies were suggested significant correlation between measured peak growth hormone and both peak (H^+) and peak lactate concentration but the highest peak showed correlation only between growth hormone and H^+. Randomized double-blind experiment was carried out on active men who were administered an alkaline solution before exercise and they were compared with controls who received salty water. Venous blood samples were obtained several times before, during and post workout. The growth hormone concentration was lower in alkalosis group than in control subjects, thus it was suggested that an increase in blood hydrogen ion concentration may be responsible for growth hormone secretion during acute high-intensity anaerobic exercise. Even though many studies have been carried out, we don't know clearly the mechanism by which an increase in H^+ acts as a stimulus for growth hormone release (Gordon *et al*., 1994).

- Afferent signals from muscle metabolic receptors

It was speculated that neural afferent signals from receptors might participate in releasing of catecholaminergic activation. When afferent nerve activity was blocked by epidural anaesthesia, it had no effect on the growth hormone response to exercise. Anyway, it is assumed that afferent nervous activity might play a role in the regulation of growth hormone release, because increasing central motor activity might offset the reduction in afferent sensory signals. The results from the test with epidural anaesthesia suggested a bigger role of central command to the exercise-induced growth hormone release, than regulation by afferent feedback from receptors in exercising muscles (Kjaer *et al*., 1989).

- Motor center activity

As it is known, motor center activity stimulates releasing of pituitary hormones, including growth hormone. Studies which were working with the theory of importance of motor center activity for growth hormone releasing were based on the study of afferent sensory blockade by epidural anaesthesia combined with electrically induced cycling. In a further study, electrically induced leg cycling in tetraplegic patients. Growth hormone concentrations increased as a result of voluntary arm exercise was studied. Because it didn't increase due to involuntary leg stimulation, we can say that central nervous system, activity in motor center and afferent nerves from metaboceptors located in the exercising muscles are all important in growth hormone response to exercise (Kjaer *et al.*, 1987).

- A proprioceptive mechanism

There has been identified another potent pituitary growth hormone which is called bioassayable growth hormone and it is different from immunoassayable growth hormone. It can be measured in other than 22kDa GH and it is distinct from IGH. It was suggested in some studies that a proprioceptive mechanism might contribute to the regulation and release of bioassayable growth hormone (McCall *et al.*, 2000).

- Catecholamines

It is known that blood catecholamines, adrenaline (A) and noradrenalin (NA), rise with the increase of exercise intensity. In exercising humans, there exists a correlation between plasma NA and serum growth hormone concentration. But the time of peaks in A and NA was delayed by 20 min and with no relation to intensity. A linear relationship was suggested between the increment in growth hormone and the increment either in A or NA, but multiple linear regression emphasized the dominant relationship between incremental changes in growth hormone and NA. It was suggested that the increase of growth hormone secretion during higher intensity exercise might be, at least in part, driven by central adrenergic activation (Kjaer *et al.*, 1989).

- Change in core temperature

It has been predicted that core temperature has a big influence to growth hormone release, but in later studies it was suggested that the rate of rise in body temperature is more important than the magnitude of change. This has been found when 30 min of cycling was performed both at room temperature (about 23 °C) and hot conditions (about 40 °C). To increase growth hormone release, an increase in the core temperature is needed, at least by 0,6 °C. When the core temperature reaches the 38-38,5 °C the next warming has an exponential relationship between elevation in core temperature and growth hormone release (Buckler *et al.*, 1973).

▪ Oxygen demand / availability ratio

A study demonstrated that in individuals dwelling at sea level, i.e. non--adapted to hypoxia, occurred a greater growth hormone response to exercise, compared to that who trained under acute hypoxic conditions. But in fact, this study reported a higher blood lactate response under hypoxic conditions. So, it was suggested that the growth hormone response to exercise is probably proportional to the ratio of oxygen demand to oxygen availability. This idea was applied to researches which were carried out and the relationship between the growth hormone response and this ratio was suggested (Raynaud *et al*., 1981; VanHekler *et al*., 1987; VanHekler *et al*., 1984).

▪ Summary

It's clear that many factors take part to the regulation of growth hormone release to allow adaptations to the situation and reactions to environmental factors.

2.8 Excess post-exercise oxygen consumption

Excess post-exercise oxygen consumption (EPOC) is increased oxygen consumption after exercise. It is a prolonged process after the end of physical exercise. From an individual's point of view, they sweat more, have a quick heartbeat and experience slightly accelerated and deeper breathing. From the molecular point of view, this is the phase of metabolism which lasts up to several hours and involves aerobic metabolism. Muscle and blood oxygen stores are restored, levels of various hormones are elevated, and body temperature, heart rate and breathing rate decrease. Some other processes, such as metabolism of lactate in the liver, muscle glycogen supplementation, protein breakdown and subsequent increased proteosynthesis are also involved (Kreamer et al., 2016i).

2.8.1 EPOC after aerobic exercise

Any physical activity can cause EPOC, but the certain length of the EPOC phase differs. Several factors influence the volume of EPOC at aerobic load. The first is the intensity of the given physical activity, most often expressed as a percentage of the maximum oxygen consumption (VO_2max)

or of the maximum heart rate. According to studies which address with this topic, we can say that after higher load intensities the EPOC value will be higher than a lower intensity load. In one of the Bahr's and Sejersteda's classical studies (1991), a group of participants (6 men) carried out a bicycle ride for 80 minutes with three different load intensities (29% VO_2max, 50% VO_2max and 75% VO_2max). After the lowest intensity ride, the EPOC lasted for 18 minutes and represented approximately 26.5 kJ. EPOC averaged 198 minutes at mean intensity and totalled 116 kJ. After the highest intensity exercise, EPOC lasted 10.5 hours on avarage and overall it represented 612 kJ. The following simple equation is used for this conversion (Swain *et al.*, 1994): % maximum heart rate = 0.6463$*$% VO_2max + 37.182. The second factor contributing to the volume of EPOC under load is the duration of this load. Chad and Wenger (1988) investigated the effect of the length of the load on EPOC. Study participants (3 males and 3 females) at 70% VO_2max load exercised for 30, 45 and 60 minutes. The minimum EPOC took 128 minutes and consisted of 134 kJ. After 45 minutes, the EPOC lasted 204 minutes, and the burnt energy thus equaled 303 kJ. Finally, after the longest activity lasting 60 minutes, the EPOC lasted 455 minutes and represented 671 kJ. Participants in the study who underwent the activity lasting half an hour burned energy equivalent to energy stored in less than 8 grams of carbohydrates over the next 2 hours after the load.

2.8.2 EPOC after an interval training

High intensity endurance training is often described as an activity associated with a long and long-lasting EPOC. Bahr et al. (1992) have studied various protocols of interval loads on 6 men in their study. It was a ride on a bicycle at an intensity of 108% VO_2max. These protocols were 1x2 minutes, 2x2 minutes with a 3-minute pause between these two intervals and last 3x2 minutes again with pauses of 3 minutes. The results of the study are summarized in the figure below. If we compare the results of the study mentioned above with the results of this study, the EPOC was comparable to a 30-minute load at a rate of 70% (303 kJ) with a load of 3x 2 minutes at 108% VO_2max (331 kJ). However, we must realize that even if EPOC values are comparable or slightly higher at intervals, much more energy is burned during physical activity itself.

Figure 7 An interval training and EPOC phase

Interval	Intensity (VO_2 max)	Duration of EPOC (min)	EPOC
1x2 min	108%	30	114 kJ
2x2 min	108%	60	136 kJ
3x2 min	108%	240	331 kJ

2.8.3 EPOC after strenght training

Only a few studies of resistance training were methodologically well-built and well-understood to tell us about the influence of strength training on EPOC. In the first, Schuenke's study (2002), which is described, participants (7 men) performed circuit training with bench press exercises, squats, and 4 series of 10 repetitions of power-ups until fail. The results of the study showed that the Resting Metabolic Rate, i.e. the quiescent energy output, was significantly increased for 38 hours after training by 10% on avarage, but a more precise description of the results in the study is unfortunately missing. These newer studies do not indicate their results as an absolute number of excess kilojoules or oxygen (each liter of oxygen is equivalent to 20.3 kJ), but as an increase in the rest of the energy consumption, which is, in essence, the energy represented by the EPOC value.

The results of another study resulted in RMR values, which increased by 15.1% after 24 hours in trained patients and by 20.1% in untrained individuals. They were still elevated 48 hours after training by 9% and 13.3% compare to baseline values. If we look at a specific increase in kilojoules, the less trained group of participants reached an average of almost 2000 kJ. These results are consistent with claims that increased proteosynthesis due to muscle fiber damage during strength training is associated with high energy requirements, and that large muscles are able to grow up to 48 hours after training (Chesley *et al*., 1992; Hather *et al*., 1991).

3. HYPOTHESIS

The GH response to exercise is proportional to:

1) the ratio of total energy demand (oxygen demand) of the exercise and the energy deriving from aerobic metabolism (oxygen availability)

2) the ratio of oxygen deficit, meaning the energy exchanged to accomplish the exercise deriving from high energy phosphates (anaerobic alactic metabolism) to oxygen availability

There is a specific relationship between the GH production or the GH increment and the slow EPOC.

4. EXPERIMENTAL PART

4.1 Participants

4.1.1 Informed constent

Sixteen male subjects, aged between 21 and 37, were recruited for this study after a health and fitness screening and signing a written informed consent to participate.

4.2 Methods

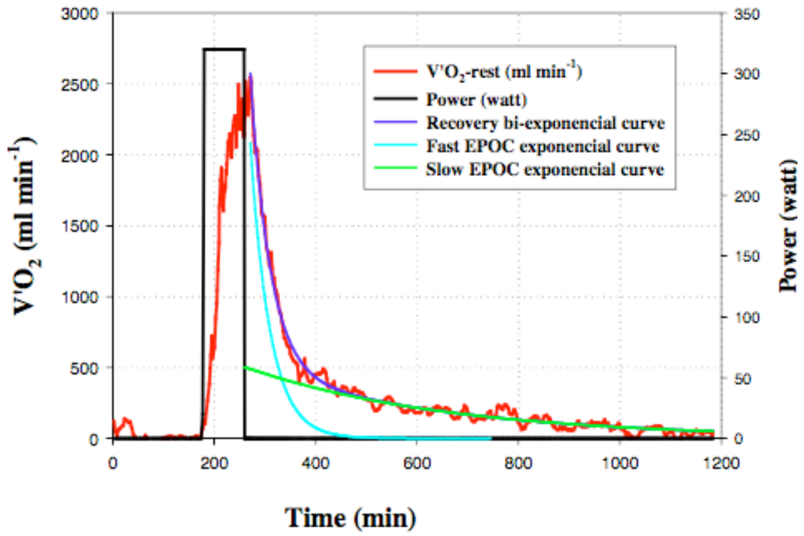
4.2.1 Tests

Participants underwent to an arm cranking ergometer (ACE) (ER800, Cosmed, Italy) maximal incremental exercise test under electrocardiographic (Delta 640, Cardioline, Italy) and metabolic monitoring (Quark b2, Cosmed, Italy; LactatePro, Arkay, Japan) to determine the cardiovascular health and to assess the accurate intensity for a 150% oxygen uptake peak (VO2 peak) constant power exercise test (ExT). The ExT was carried out up to exhaustion, monitoring and controlling the subjects at rest, during exercise and during recovery phase, with the same instruments as the previous exercise (ACE, metabolimeter, blood lactate tester, electrocardiogram) to assess the mechanical work (total work), metabolic and cardiac response and collecting blood samples to study hormonal response. A week later, a constant power, 150% VO2 peak intensity, anaerobic test up to exhaustion (AnT) was carried out to assess total mechanical work (MWtot) and GH response. To measure serum GH concentration (IRMA, HGH--RIACT, CIS Bio International, F), venous blood samples were collected before and after the ExT with the following time schedule (end of Ext identified as time “0”): -20, -5, +1, +5, +15, +30, +60, +90 minutes. To assess lactate peak, capillary blood samples were collected before and after exercise, each minute from the end of ExT until a clear lactate decrease was observed.

4.2.2 Assessment of ExT energy expenditure

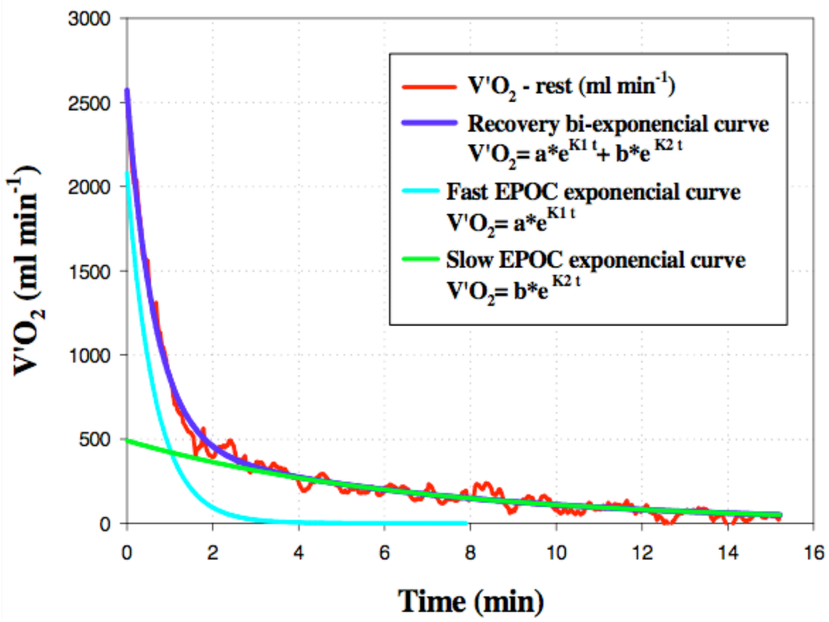
In order to determine the relative energy contributions to perform the ExT (aerobic, lactic anaerobic and alactic anaerobic), blood lactate peak and VO_2 curve was processed before, during and after the effort in accordance with di Prampero (1981) and Beneke et al. (2002). The VO_2 curve during recovery was best fitted by a bi-exponential curve to assess the mathematical coefficients for two mono-exponential curves describing first (fast) and second (slow) VO_2 declines, and named fast excess of oxygen consumption following (post) exercise (fast EPOC) and slow EPOC, respectively. The zoom in following figures shows this analysis.

Figure 8 VO_2 curve



Anaerobic test up to exhaustion (AnT – 150% VO_2peak) VO_2 curve processing during the recovery phase. The best fit curves of the O_2 flow that describe the fast and slow EPOC during recovery. Typical metabolic and cardiac response to an exhaustion exercise test (AnT) of constant power high intensity (150% VO_2 peak) up to exhaustion. Curves of oxygen consumption (VO_2), carbon dioxide production ($V'CO_2$), heart rate (HR)Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

Figure 9 Slow EPOC curve



Anaerobic test up to exhaustion (AnT – 150% VO_2peak) VO_2 curve processing during the recovery phase. The best fit curves of the O_2 flow that describe the fast and slow EPOC during recovery. Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

4.2.3 Assessment of GH production as response to ExT

GH concentration values measured at rest and after exercise were best fitted with two logarithmic curves:

$$GH(t) = a \cdot e^{-\frac{1}{2}\left[\frac{\ln\left(\frac{t}{t_0}\right)}{b}\right]^2} \text{ and } GH(t) = y_0 \cdot a \cdot e^{-\frac{1}{2}\left[\frac{\ln\left(\frac{t}{t_0}\right)}{b}\right]^2}$$

with t_0 corresponding to end of ExT, and y_0 corresponding to GH basal value at t_0-compute GH production with the curve that fitted data most appropriately.

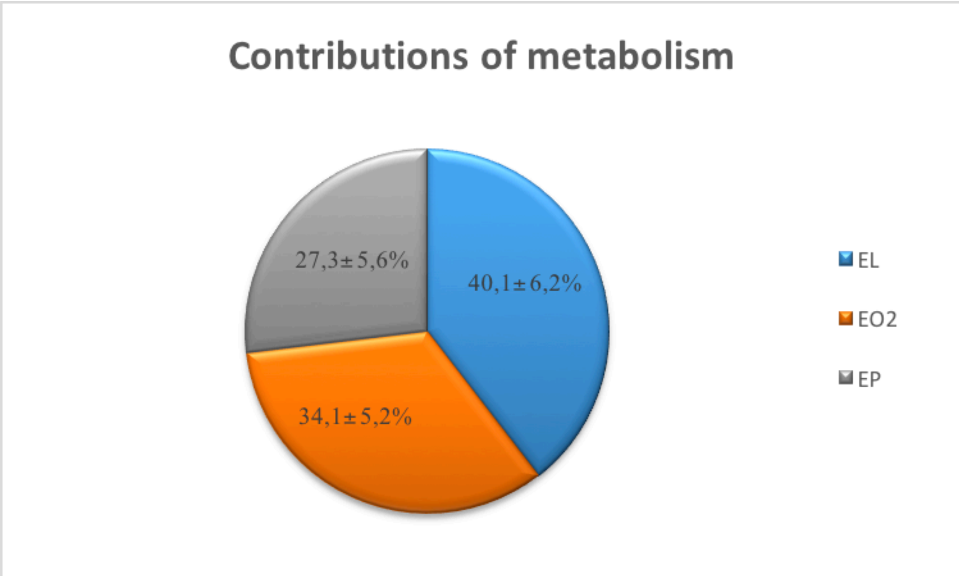
4.2.4 Statistical analysis

All the values measured in this phase of the search are shown like averages and standard deviation. The analyses statistics have been carried out by the software "Statistics", version 6,0 (StatSoft Inc. USA) and the correlations have been estimated by Spearman correlation test. The graphical representations have been carried out by the program "SigmaPlot 2004", version 9,0 (SPSS Inc., USA), the same program is used to characterize the exponential curves of the metabolic adjustment (the oxygen consumption) in the recovery period (see methods on "fast and slow EPOC"). By the program "Microsoft Office Excel 2003", version 11.5612.5606 (Microsoft Corporation, USA) have been calculate the integrals of the single metabolic response to calculate the area under the curve of the oxygen consumption during effort (volume of relative oxygen to the energetic contribution of aerobic metabolism) and during recovery (volume of relative oxygen to the energetic contribution of the anaerobic alactacid metabolism).

5. RESULTS

The exercise test was carried out at 277±57.9 watt, it determined a total mechanical work of 25.2±7.3 kJ and lasted 91±19.5 seconds. The total energy expenditure was equal to 139±36.7 kJ. This number corresponds to the term oxygen demand and it consists of three metabolisms which are anaerobic alactic energy (high energy phosphates) (EP), anaerobic lactic energy (EL) and aerobic energy (oxygen availability –EO_2).

Figure 10 Contributions of metabolism



Contribution of anaerobic alactic energy (EL), anaerobic lactic energy (EL) and aerobic energy(EO_2). Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

From basal values (0.29±0,44 μg/l) GH increased in 27±11 minutes after an exercise test to values equal to 7.1±3.55 μg/l, which shows a significant increment as response to exercise.

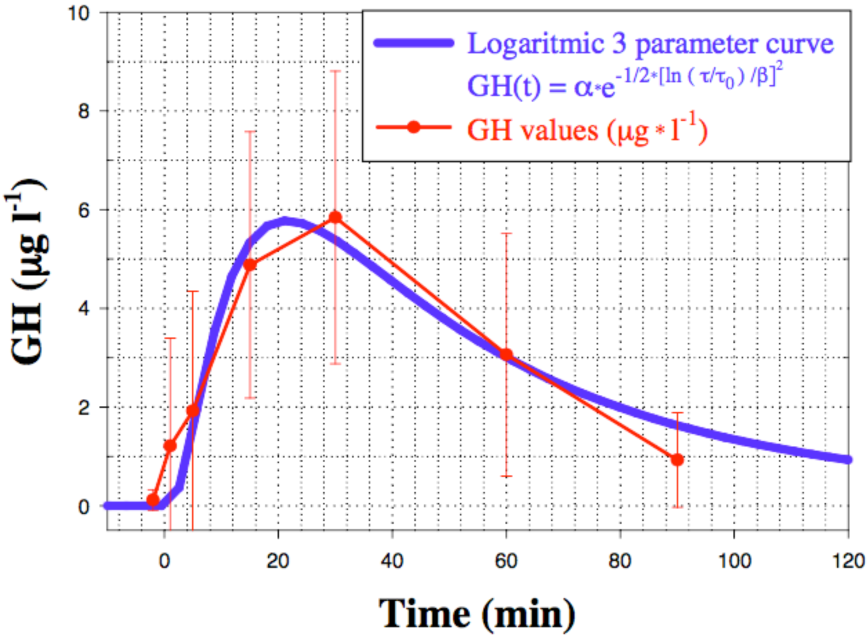
GH concentration values measured at rest and as response to exercise. Time "0" corresponds to the end of exercise. There are two logarithmic curves.

$$GH\ (t) = \alpha \cdot e^{[-\frac{1}{2}*\left(\frac{\ln\left(\frac{\tau}{\tau_O}\right)}{\beta}\right)^2]}$$

$$GH(t) = y_o + \alpha * e^{[-\frac{1}{2}*\left(\frac{\ln\left(\frac{\tau}{\tau_0}\right)}{\beta}\right)^2]}$$

The following figure shows GH response in time.

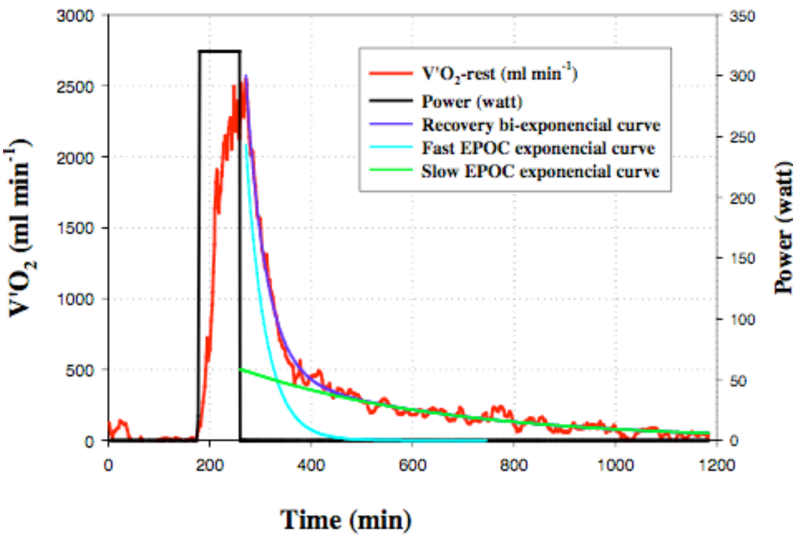
Figure 11 Kinetics of GH respons to high intensity exercise



GH kinetics of the response to high intensity training. Time 0 is the time of the end of exercise. In the figure, mean values, the best fit curves and standard deviation are shown. The average production of growth hormone was equal to 408±230 μl/min. Data were analysed from the area under the GH concentration curve. Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

The following figure describes a curve of VO_2 in time and power in time using equations previously mentioned.

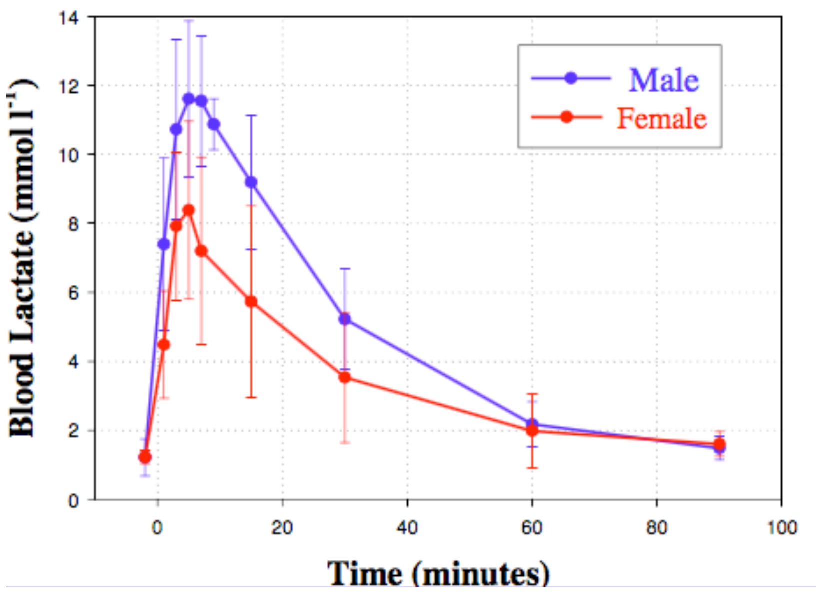
Figure 12 Results of an exhaustion test (150% VO_2 peak)



Typical metabolic and cardiac response to an exhaustion exercise test (AnT) of constant power high intensity (150% VO_2 peak) up to exhaustion. Curves of oxygen consumption (VO_2), carbon dioxide production ($V'CO_2$), heart rate (HR). Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

Blood lactate curve is described in the following figure.

Figure 13 Results of an exhaustion test (150% VO_2 peak)



Curve of blood lactate levels are shown in the Figure 13. Time 0 means the end of exercise. The biggest blood lactate response is around the time of 6 minutes after the end of exercise. The peak lactate is 12,3±1,9 mmol/l in men Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

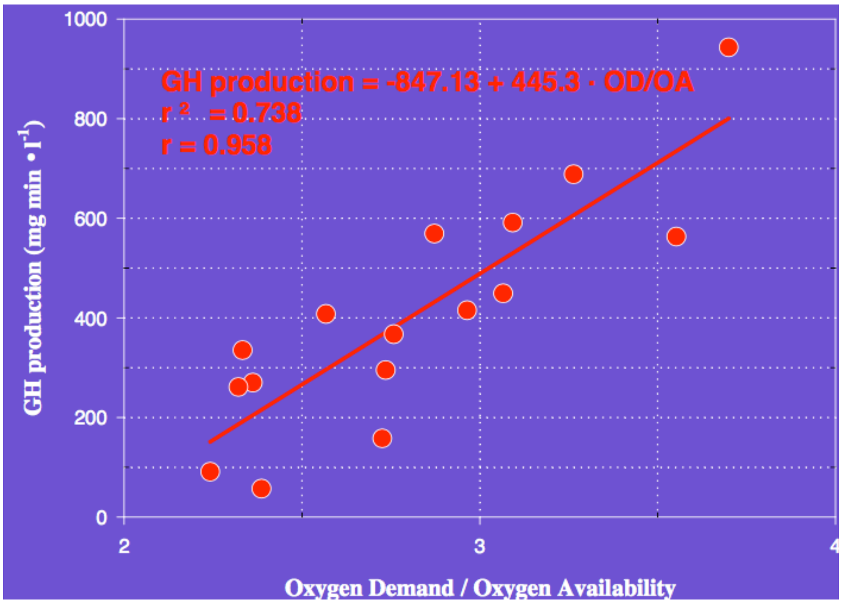
Figure 14 Results of an exhaustion test (150% VO_2 peak)

Subjects	Highest VO_2 (ml/min/kg)	Highest HR (b/min)	Power (watt)	AnT duration (s)	Total mechanical work (kJ)	Lactate peak (mmol/l)
Men	31.7 ±4.86	178±15	277.6±57.9	91±19.5	25.2±7.3	12.3±1.9

Data obtained during an exhaustion exercise test (AnT) of constant power high intensity (150% VO_2 peak) up to exhaustion. Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

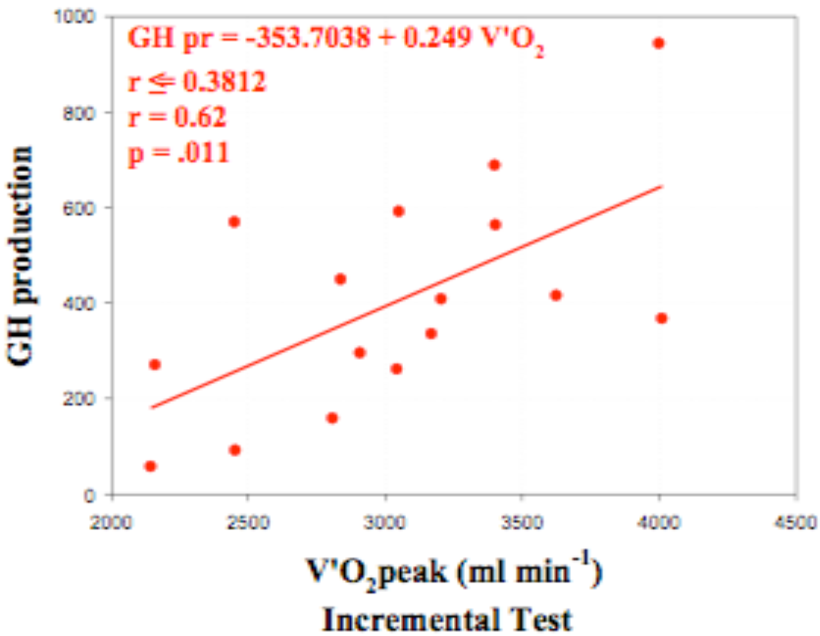
Linear correlation between GH production and oxygen demand/ oxygen availability ratio

Figure 15 Linear correlation between GH production and ratio between oxygen demand and oxygen availability



Production of growth hormone correlates with the ratio of oxygen demand to oxygen availability. Linear correlation is highly significat – r= 0.958. Where "r" stands for variance (<0,1>; 0= full variance, 1= full linearity) Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

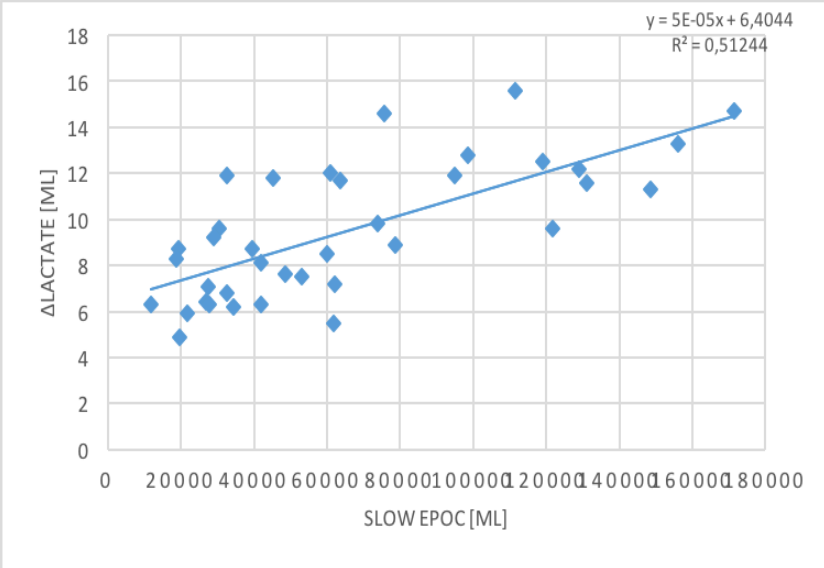
Figure 16 Relationship between GH and VO_2 peak at the incremental test



Production of growth hormone correlates with VO_2 peak expressed in absolute values (r=0,62). Where "r" stands for variance (<0,1>; 0= full variance, 1= full linearity). Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

In the Figure 17, there is a linear correlation between lactate and slow EPOC shown.

Figure 17 Linear correlation between lactate increment and slow EPOC



There is a linear correlation between lactate increment and oxygen consumption during the slow EPOC. Linear correlation is highly significant –r= 0,72. Where "r" stands for variance (<0,1>; 0= full variance, 1= full linearity). Data were obtained and processed in prof. Marco Bernardi's laboratory, with permission.

6. DISCUSSION

The study shows that exercising up to exhaustion (at 150% VO_2 peak) can induce a relevant GH increment and production. It seems that GH release is regulated by the energy metabolism, which is directly correlated with EP and inversely correlated with EO_2.

The results confirm the fact that GH response to exercise is dependent on an oxygen deficit at the beginning of exercise and explain the correlation between GH response to exercise and the ratio of oxygen demand to oxygen availability, which explains the direct relationship between GH response and oxygen deficit at the beginning of exercise. Our study explains why GH response is greater and faster in hypoxic and altitude exercise than at sea level (Raynaud *et al.*, 1981). The present study on GH response to constant power arm cranking ergometer exercise at an intensity equal to 150% of the VO_2 peak and carried out up to exhaustion confirms the results of the authors who found in submaximal lower body exercise and in resistance exercises a positive correlation between GH changes and the corresponding oxygen demand/availability ratio (VanHelder *et al.*, 1987). Our method allows counting energy expenditure exactly and we can state how much it is. This is an advantage over other thesis studing all out test in which power is changing.

Many studies (Bahr et al., 1992; Laforgia, 1997; Schuenke, 2002) were carried out to study EPOC phase after interval training. Many of them confirmed that energy expenditure in EPOC phase, i.e. after the end of high intensity interval training, is just a small fraction of the energy consumed by the exercise. To discuss our results, we can examine the results of a study carried out by Laforgia (1997), who compared the EPOC value of 8 trained men after a 20x1 minute interval with 2 minute intervals of 105% VO_2max with a duration of 30 minutes and an intensity of 70% VO_2max. This study is interesting because, as one of the few, it shows us through the results how much of the total burnt energy represents the EPOC value. These results show that EPOC generated at intervals does not play a role, as it is often claimed, and the share of this energy in the total energy released by motion activity (energy burned during EPOC + the activity alone) is only a fraction of it.

However, our study shows that it is not just about the energy expenditure in EPOC phase but also about the GH released in this phase.

Our study confirms what Chad and Wenger said in their study, i.e. that the EPOC value is most affected by the duration of physical activity and its intensity expressed as a percentage of VO_2max or as a percentage of the maximum pulse frequency. This means the longer and the more intense physical activity, the higher EPOC.

Dolezal *et al*. came up with a study in which the participants were separated into two groups according to their physical fitness status. He confirmed that physical fitness status may have an effect on EPOC. Lower physical fitness status may mean higher muscle damage, increased energy demands for regeneration and longer time needed to return to rest after exercise. This leads to a recommendation that beginners at the gym should not copy the training plans of their more experienced colleagues since these would be too demanding for them and they might prevent them from further training. Moreover, it would result in the need for putting more emphasis on nutrition and replenishment. But it also confirmed the results from our study. We state that the higher percentage of VO_2max of an individual, the higher EPOC value. With the knowledge that individuals with lower fitness status have a lower VO_2 max value, we can confirm the results of his experiment.

With this new knowledge, we can set up the training in which growth hormone response to specific exercise is very high but corresponds with the individual fitness status. With that theoretical knowledge that GH has a lipolytic effect in adults, and that after high intensity interval training growth hormone production is significantly higher, we can change the dogma speaking about long lasting moderate trainings as of a way of reducing fat mass. If we take a look at the increasing number of obese or overweight people and consider current lifestyle, when people are still in a hurry all the time and do not have a time for long-lasting and uninteresting exercise, we can design short--lasting, but very effective training sessions for each individual. It would bring many health--related benefits, such as a decrease in resting blood pressure, thus reducing the risk of developing diseases (e.g. cardiovascular diseases), and also fitness related benefits, such as increased lactate threshold, improved agility, coordination, speed and maximal strength. Some physical adaptation can bring both fitness and health benefits, such as the increased peak of oxygen consumption, which can increase performance in endurance sports and also represents a strong predictor of overall mortality (Kesaniemi *et al*., 2001). What is more, shorter training can bring higher convenience because it fits better into our hurried lives. All these benefits confirm that exercise, especially high intensity interval training, can be considered medicine.

7. Conclusion

The study suggests that high intensity, short duration exercise is able to determine a relevant response of growth hormone. This response is proportional to the ratio of total energy expenditure of the exercise to the energy deriving from anaerobic metabolism (oxygen demand/oxygen availability), and also to the ratio of energy deriving from anaerobic alactacid metabolism and oxygen availability.

The study suggests the ratio between the us of high energy phosphates and the lack of oxygen as a stimulus for the increment of growth hormone and its production after exercise. In an environment with a lack of oxygen and use high energy phosphates muscles determine GH release.

The study shows that aerobic fitness status characterized by higher VO_2 peak has a positive feedback effect on the GH response to high intensity exercise. Based on the knowledge about lipolityc effect of GH, we can assume that high intensity interval training can improve body composition by means of reducing fat tissue.

8. References

American College of Sports Medicine ACMS's Guidelines for Exercise testing and Prescription 9th ed. [Book]. - [s.l.] : Lippincott Williams&Wilkins, 2013

American College of Sports Medicine ACSM's Guidelines for Exercise Testing and Prescription [Book]. - [s.l.] : Lippincott Williams& Wilkins, 2010. - 8 : p. 159.

American College of Sports Medicine Position Stand, American Heart Assosiation Resommendations for cardiovascular screeneng, staffing, and emergency policies at health/fitness facilities [Journal] // Med Sci Sports Exerc. - 1998. - 6 : Vol. 30. - pp. 1009-18

American College of Sports Medicine Progression models in resistance training for healthy adults [Journal] // Medicine and Science in Sports and Exercise. - 2009. - Vol. 42. - pp. 687-708.

Atterhög J.H. Jonsson B., Samuelsson R. Exercise testing: a prospective study of complication rates. [Journal] // American Heart Journal. - 1979. - 5 : Vol. 98. - pp. 572-579.

Bahr R., Grønnerød O. & Sejersted O.M Effect of supramaximal exercise on excess postexercise O2 consumption. [Journal] // Medicine and Science in Sports and Exercise. - 1992. - 1 : Vol. 24. - pp. 66-71

Bahr R., Sejersted O.M. Effect of intensity of exercise on excess postexercise O2 consumption [Journal] // Metabolism: Clinical and Experimental.. - 1991. - 8 : Vol. 40. - pp. 836-841.

Booth Frank W. Lees S.J. Fundamental questions about genes, inactivity, and chronic diseases. [Journal] // Physiol Genomics. - 2007. - 2 : Vol. 28. - pp. 146-157.

Booth Frank W. Manu V. Chakravarthy and Espen E. Spangenburg Exercise and gene expression: physiological regulation of the human genome through physical activity [Journal] // The Journal of Physiology. - 2002. - pp. 399-411.

Booth Frank W. P.Darrell Neufer Exercise Controls Gene Expression [Journal] // American Scientist. - 2005. - Vol. 93. - pp. 28-35.

Buckler The relationship between changes in plasma growth hormone levels and body temperature occurring with exercise in man. [Journal] // Biomedicine. - 1973. - 5 : Vol. 19. - pp. 193-197

Calle Eugenia E. Ph.D., Carmen Rodriguez, M.D., M.P.H., Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults [Journal] // The New England Journal of Medicine. - 2003. - Vol. 348. - pp. 1625-1638.

Caspersen C.J. Powell K.E., Christenson G.M., Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research [Report] / Public Health Report. - Washington D.C. : [s.n.], 1985. - pp. 126-131.

Cawley John Meyerhoefer Chad The medical care costs of obesity: An instrumental variables approach [Journal] // Journal of Health Economics. - 2012. - Vol. 31. - pp. 219-230.

Chad K.E. ,Wenger H.A The effect of exercise duration on the exercise and post-exercise oxygen consumption [Journal] // anadian Journal of Sport Sciences = Journal Canadien Des Sciences Du Sport. - 1988. - 4 : Vol. 13. - pp. 1383-1388.

Chesley A. MacDougali J.D., Tarnopolsky M.A., Atkinson S.A., et al Changes in human muscle protein synthesis after resistanceexercise. [Journal] // Journal of Applied Physiology. - 1992. - 4 : Vol. 73. - pp. 1383-1388.

Cordain L. Gotshall R.W., Eaton S.B. Physical activity, energy expenditure and fitness: an evolutionary perspective [Journal] // International Journal of Sports Medicine. - 1998. - 5 : Vol. 19. - pp. 328-35.

Council of Europe, Committee of ministers Charter of Sport [Report]. - Strasbourg : [s.n.], 1992.

Dolezal Bertt A. J.A.P. Effect of exercise intensity, duration and mode on post-exercise oxygen consumption [Journal] // Sports Medicine. - 14 : Vol. 33. - pp. 1037-1060

Eaton S.B., Lindeberg S., Konner M.J., Mysterud I., Cordain Evolutionary health promotion [Journal] // Preventive Medicine. - 2002. - 2 : Vol. 34. - pp. 109-118

Feskanich D. Willett W., Colditz G. Walking and leisure-time activity and risk of hip fracture in postmenopausal women [Journal] // JAMA. - 2002. - 18 : Vol. 288. - pp. 2300-2306

Fontaine K.R. Redden D.T., Wang C., Westfall A.O., Allison D.B. Years of life lost due to obesity [Journal] // JAMA. - 2003. - 2 : Vol. 289. - pp. 187-193.

Fox Interval training [Journal] // Bulletin of the Hospital dor the Joint diseases. - 1979. - Vol. 40. - pp. 64-71.

Galliven E.A. Singh A., Michelson D., Bina S., Gold P.W., Deuster P.A. Hormonal and metabolic responses to exercise across time of day and menstrual cycle phase [Journal] // Journal of Applied Physiology. - 1985. - 6 : Vol. 83. - pp. 1822-31.

Gordon S.E. Kraemer W.J., Vos N.H., Lynch J.M., Knuttgen H.G. Effect of acid-base balance on the growth hormone response to acute high-intensity cycle exercise [Journal] // Journal of Applied Physiology. - 1994. - 2 : Vol. 76. - pp. 821-829.

Green D.J. O'Driscoll G., Joyner M.J., Cable N.T. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? [Journal] // Journal of Applied Physioloy. - 1985. - 2 : Vol. 105. - pp. 766-768.

Hallal P.C. Andersen L.B., Bull F.C., Guthold R., Haskell W., Ekelund U. and Group Lancet Physical Activity Series Working Global physical activity levels: surveillance progress, pitfalls, and prospects [Journal] // Lancet. - 2012. - Vol. 380. - pp. 247-257.

Haskell Cardiovascular complications during exercise training of cardiac patients [Journal] // Circulation. - 1978. - 2 : Vol. 57. - pp. 920-924.

Haskell W.L. Lee I.M., Pate R.R., Powell K.E., Blair S.N., Franklin B.A., Macera C.A., Heath G.W., Thompson P.D., Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association [Journal] // Medicine and Science in sports exercise. - 2007. - 8 : Vol. 39. - pp. 1423-1434.

Hather B.M. Tesch P.A., Buchanan P. & Dudley G.A Influence of eccentric actions on skeletal muscle adaptations to resistance training [Journal] // Acta Physiologica Scandinavica. - 1991. - 12 : Vol. 143. - pp. 1247-1264

Helgerud J. Høydal K., Wang E., Karlsen T., Berg P., Bjerkaas M., Simonsen T., Helgesen C., Hjorth N., Bach R., Hoff J. Aerobic high-intensity intervals improve VO2max more than moderate training [Journal] // Medicine and science in sports exercise. - 2007. - 4 : Vol. 39. - pp. 665-671.

Ho K.Y. Evans W.S., Blizzard R.M., Veldhuis J.D., Merriam G.R., Samojlik E., Furlanetto R., Rogol A.D., Kaiser D.L., Thorner M.O. Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations [Journal] // Journal of clinical endocrinology and metabolism . - 1987. - 1 : Vol. 64. - pp. 51-58

Hollis C.K., Courtney J. Stevens, Renee E. Magnan, Nicole Harlaar, Kent E. Hutchison, Angela D. Bryan Genetic Influences on Physiological and Subjective Responses to an Aerobic Exercise Session among Sedentary Adults [Journal] // J Cancer Epidemiol . - 2012. - p. 12

Internetional Sport and Culture Assosiation The Costs of Inactivity in Europe [Report]. - London : CEBR, 2015.

Iranmanesh A. Lizarralde G., Veldhuis J.D. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men [Journal] // Journal of clinical endocrinology and metabolism . - 1991. - 5 : Vol. 73. - pp. 1081-1088

Jenkins Paul Growth hormone and exercise: Physiology, use and abuse // Growth Hormone & IGF Research. - 2001. - 1. - Vol. 11. - pp. 71-77.

Kanaley J.A. Weatherup-Dentes M.M., Jaynes E.B., Hartman M.L. Obesity attenuates the growth hormone response to exercise [Journal] // Journal of clinical endocrinology and metabolism . - 1999. - 9 : Vol. 84. - pp. 3156-3161.

Karp J.R. Interval training for the fitness professional [Journal] // Strenght&Conditioning Journal. - 2000. - Vol. 22. - pp. 64-69.

Katzmarzyk P.T. Church T.S., Janssen I., Ross R., Blair S.N. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness [Journal] // Diabetes Care. - 2005. - 2 : Vol. 28. - pp. 391-397.

Kavouras S.A. Panagiotakos D.B., Pitsavos C., Chrysohoou C., Anastasiou C.A., Lentzas Y., Stefanadis C. Physical activity, obesity status, and glycemic control: The ATTICA study. [Journal] // Medicine and science in sports exercise. - 2007. - 4 : Vol. 39. - pp. 606-611

Kesaniemi Y.K. Danforth E. Jr., Jensen M.D., Kopelman P.G., Lefèbvre P., Reeder B.A. Dose-response issues concerning physical activity and health: an evidence-based symposium [Journal] // Medicine and science in sports exercise. - 2001. - 6 : Vol. 33. - pp. 351-358

Kjaer M. Epinephrine and some other hormonal responses to exercise in man: with special reference to physical training. [Journal] // International journal of sports medicine. - 1989. - 1 : Vol. 10. - pp. 2-15.

Kjaer M. Secher N.H, Bach F.W., Galbo H Role of motor center activity for hormonal changes and substrate mobilization in humans [Journal] // American Journal of physiology. - 1987. - Vol. 253. - pp. 687-695

Kodama S. Saito K., Tanaka S., Maki M., Yachi Y., Asumi M., Sugawara A., Totsuka K., Shimano H., Ohashi Y., Yamada N., Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. [Journal] // JAMA. - 2009. - 19 : Vol. 301. - pp. 2024-2035.

Kraemer William J. Steven J. Fleck, Michael R. Deschenes Exercise physiology: Integrating Theory and Application [Book] / ed. Lippincott Williams & Wilkins 2015. – 2016h. - second.ed.,147

Kraemer William J. Steven J. Fleck, Michael R. Deschenes Exercise physiology: Integrating Theory and Application [Book] / ed. Lippincott Williams & Wilkins 2015. – 2016a. - second.ed.,348

Kraemer William J. Steven J. Fleck, Michael R. Deschenes Exercise physiology: Integrating Theory and Application [Book] / ed. Lippincott Williams & Wilkins 2015. – 2016b. – second ed., 347-348

Kraemer William J. Steven J. Fleck, Michael R. Deschenes Exercise physiology: Integrating Theory and Application [Book] / ed. Lippincott Williams & Wilkins 2015. – 2016c. – second ed., 380-393

Kraemer William J. Steven J. Fleck, Michael R. Deschenes Exercise physiology: Integrating Theory and Application [Book] / ed. Lippincott Williams & Wilkins 2015. – 2016d. – second ed., 209-244

Kraemer William J. Steven J. Fleck, Michael R. Deschenes Exercise physiology: Integrating Theory and Application [Book] / ed. Lippincott Williams & Wilkins 2015. – 2016i. – second ed., 63-65

Laforgia J. Withers R.T., Shipp N.J. & Gore C.J. Comparison of energy expenditure elevations after submaximal and supramaximal running [Journal] // Journal of Applied Physiology. - 1997. - 2 : Vol. 82. - pp. 661-666.

Lee I.M. Shiroma E.J., Lobelo F., Puska P., Blair S.N., Katzmarzyk P.T. and Group Lancet Physical Activity Series Working Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. [Journal] // Lancet. - 2012. - Vol. 380. - pp. 219-29.

Leitzmann M.F. Rimm E.B., Willett W.C., Spiegelman D., Grodstein F., Stampfer M.J., Colditz G.A., Giovannucci E. Recreational physical activity and the risk of cholecystectomy in women. [Journal] // The New England journal of medicine . - 1999. - 11 : Vol. 341. - pp. 777-784.

Manson JE1 Greenland P, LaCroix AZ, Stefanick ML, Mouton C.P., Oberman A., Perri M.G., Sheps D.S., Pettinger M.B., Siscovick D.S. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. [Journal] // The New England journal of medicine. - 2002. - 10 : Vol. 347. - pp. 716-725.

McCall G.E. Grindeland R.E., Roy R.R., Edgerton V.R. Muscle afferent activity modulates bioassayable growth hormone in human plasma. [Journal] // Journal of Applied physiology. - 2000. - 3 : Vol. 89. - pp. 1137-1141.

Meckel Y. Gefen Y., Nemet D., Eliakim A. Influence of short vs. long repetition sprint training on selected fitness components in young soccer players [Journal] // Journal of strenght and conditioning research . - 2012. - 7 : Vol. 26. - pp. 1845-1851.

Müller E.E. Locatelli V., Cocchi D. Neuroendocrine control of growth hormone secretion. [Journal] // Physiological reviews. - 1999. - 2 : Vol. 79. - pp. 511-607.

Nader P.R. Bradley R.H., Houts R.M., McRitchie S.L., O'Brien M. Moderate-to-vigorous physical activity from ages 9 to 15 years [Journal] // JAMA. - 2008. - 3 : Vol. 300. - pp. 295-305.

National institute of Health Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults [Report]. - [s.l.] : Am J Clin Nutr, 1998. - pp. 899-917.

Ode J.J. Pivarnik J.M., Reeves M.J., Knous J.L. Body mass index as a predictor of percent fat in college athletes and nonathletes [Journal] // Medicine and science in sports exercise. - 2007. - 3 : Vol. 39. - pp. 403-409.

Pérusse L.&Bouchard C. Genotype-environment interaction in human obesity. [Journal] // Nutrition reviews. - 1999. - 2 : Vol. 57. - pp. 31-37.

Pi-Sunyer F.X. The obesity epidemic: pathophysiology and consequences of obesity. [Journal] // Obesity research. - 2002. - Vol. 10. - pp. 97-104.

Pritzlaff C.J. Wideman L., Weltman J.Y., Abbott R.D., Gutgesell M.E., Hartman M.L., Veldhuis J.D., Weltman A. Impact of acute exercise intensity on pulsatile growth hormone release in men. [Journal] // Journal of Applied physiology. - 1999. - 2 : Vol. 87. - pp. 498-504

Pritzlaff-Roy C.J. Widemen L., Weltman J.Y., Abbott R., Gutgesell M., Hartman M.L., Veldhuis J.D., Weltman A. Gender governs the relationship between exercise intensity and growth hormone release in young adults. [Journal] // Journal of applied physiology. - 2002. - 92 : Vol. 1985. - p. 5

Proper K.I. van den Heuvel S.G., De Vroome E.M,, Hildebrandt V.H., Van der Beek A.J. Dose-response relation between physical activity and sick leave. [Journal] // British journal of sports medicine. - 2006. - 2 : Vol. 40. - pp. 173-178.

Pyka G. Wiswell R.A., Marcus R. Age-dependent effect of resistance exercise on growth hormone secretion in people [Journal] // Journal of clinical endocrinology and metabolism. - 1992. - 2 : Vol. 75. - pp. 404-407.

Raastad T. Bjøro T., Hallén J. Hormonal responses to high- and moderate-intensity strength exercise [Journal] // European journal of applied physiology. - 2000. - 1-2 : Vol. 82. - pp. 121-128.

Ratamess N.A. Alvar B.A., Evetoch T.K., et al. Progresion models in resistance training for healthy adults [Journal] // Medicine and science in sport and exercise. - 2009. - Vol. 42. - pp. 687-708.

Raynaud J. L. Drouet, J. P. Martineaud, J. Bordachar, J. Coudert, and J. Durand Time course of plasma growth hormone during exercise in humans at altitude [Journal] // Journal of Applied physiology. - 1981. - 2 : Vol. 50. - pp. 229-233

Rhea M.R. Alvar B.A., Burkett L.N., Single versus multiple sets for strength: a meta-analysis to address the controversy [Journal] // Research Quarterly for Exercise and Sport. - 2002. - 4 : Vol. 73. - pp. 485-8.

Riddoch C. J. Andersen, L. B., Wedderkopp, N., Harro, M., Klassonheggebø, L., Sardinha, L. B., Cooper, A. R., and Ekelund, U., Physical Activity Levels and Patterns of 9- and 15-yr-old European Children [Journal] // Medicine and Science in Sports and exercise. - 2004. - 1 : Vol. 36. - pp. 86-92.

Shuenke M. Milkat R., McBride J. Effect of an acute period of resistance exercise on excess post-exercise oxygen consumption: implications for body mass management [Journal] // European Journal of Applied Physiology. - 2002. - 5 : Vol. 86. - pp. 411-417.

Siscovick D.S. Weiss N.S., Fletcher R.H., Lasky T. The incidence of primary cardiac arrest during vigorous exercise [Journal] // The New England Journal of Medicine. - 1984. - 14 : Vol. 311. - pp. 874-877.

Stevenson B. Beyond the Classroom: Using Title IX to Measure the Return to High School Sports [Journal] // Review of Economics and Statistics. - 2010. - Vol. 92. - pp. 284-301

Stokes K. Growth hormone response to sub-maximal and sprint exercise // Growth hormone&IGF Research. - 2003. - Vol. 13. - pp. 225-238.

Stokes K.A. Nevill M.E., Cherry P.W., Hall G.M., Lakomy H.K.A, The effect of 6 weeks of sprints training on the growth hormone response to repeated maximal cycle ergonometer exercise [Journal] // J Physiol. - 2000. - p. 523.

Swedish national institute of public health Physical Activity in the Prevention and Treatment of Disease [Case]. - Sweden : [s.n.], 2010

Thompson P.D. Stern M.P., Williams P., Duncan K., Haskell W.L., Wood P.D. Death during jogging or running. A study of 18 cases [Journal] // JAMA. - 1979. - 12 : Vol. 242. - pp. 1265-1267.

Tønnessen E. Shalfawi S.A., Haugen T., Enoksen E. The effect of 40-m repeated sprint training on maximum sprinting speed, repeated sprint speed endurance, vertical jump, and aerobic capacity in young elite male soccer players [Journal] // Journal od strenght and conditioning research. - 2011. - 9 : Vol. 25. - pp. 2364-2370.

U.S. Department of Health and Human Services Physical Activity Guidlines [Report] / USDHHS ; Advisory Committee. - Washington, D.C. : [s.n.], 2008.

U.S. Department of Health and Human Services Physical Activity Guidlines [Report] / USDHHS ; Advisory Committee. - Washington, D.C. : [s.n.], 2001

Vahl N. Jorgensen J.O.L., Jurik A., Christiansen J.S., Abdominal adiposity and physical fitness are major determinants of the age- associated decline in stimulated GH secretion in healthy adults [Journal] // Journal of clinical endocirnology and metabolism. - 1996. - 6 : Vol. 81. - pp. 2209-2215.

Vanhelder W.P. Goode R.C., Radomski M.W. Effect of anaerobic and aerobic exercise of equal duration and work expenditure on plasma growth hormone levels [Journal] // European Journal of Applied Physiology and occupational physiology. - 1984. - 3 : Vol. 52. - pp. 255-257.

VanHelder W.P. K. CaseyM. W. Radomski Regulation of growth hormone during exercise by oxygen demand and availability [Journal] // European journal of applied physiology. - 1987. - 6 : Vol. 56. - pp. 628-632.

Veldhuis J.D., Weltman A. Gender governs the relationship between exercise intensity and growth hormone release in young adults. [Journal] // Journal of applied physiology. - 2002. - 92 : Vol. 1985. - p. 5.

Waring C.D. Vicinanza C., Papalamprou A., Smith A.J., Purushothaman S, Goldspink D.F., Nadal-Ginard B., Torella D., Ellison G.M. The adult heart responds to increased workload with physiologic hypertrophy, cardiac stem cell activation, and new myocyte formation. [Journal] // European heart journal . - 2014. - 39 : Vol. 35. - pp. 2722-2731

Weeks K.L. McMullen J.R. The athlete's heart vs. the failing heart: can signaling explain the two distinct outcomes? [Journal] // Physiology. - 2011. - 2 : Vol. 26. - pp. 97-105.

Weston K.S. Wisløff U., Coombes J.S. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. [Journal] // British journal of sports medicine. - 2014. - 16 : Vol. 48. - pp. 1227-1234

Whaley Mitchell H. [et al.] ACSM's guidelines for exercise testing and prescription 7th edition [Book] / ed. Philadelphia Pa. : Lippincott Williams & Wilkins, ©2006. - 2006

Wilson M. O'Hanlon R., Prasad S.,et al Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes [Journal] // J Appl Physiol . - 2011. - 6 : Vol. 110. - pp. 1622-1626

Withrow D. Alter D.A. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. [Journal] // Obesity review. - 2011. - 2 : Vol. 12. - pp. 131-141.

Wong S.L. Katzmarzyk P., Nichaman M.Z., Church T.S., Blair S.N., Ross R. Cardiorespiratory fitness is associated with lower abdominal fat independent of body mass index. [Journal] // Medicine and Science in sports and exercise. - 2004. - 2 : Vol. 36. - pp. 286-291

9. LIST OF ABBREVIATIONS

A	adrenalin
ACE	arm cranking ergometer
AnT	exhaustion test
ATP	adenosine triphosphate
BMI	body mass index
DEXA	dual-energy x-ray absorptiometry
DM2	diabetes mellitus the second type
EL	anaerobic lactic energy
EO_2	aerobic energy
EP	high energy phosphates
EPOC	excess post-oxygen consumption
ExT	exercise test
FFM	fat- free mass
FM	fat mass
GH	growth hormone
GHIH	growth hormone-inhibiting hormone
GHRH	growth hormone-releasing hormone
H^+	hydrogen ion
HDL	high- density lipoprotein
HIIT	high-intensity interval training
HR_{max}	maximal heart rate
HRR	heart rate reserve
IGF	insulin-like growth factor
METs	metabolic equivalents
NA	noradrenalin
NO	nitrogen oxide
PPARδ	peroxisome proliferator-activated receptor delta
RM	repetition maximum
TBM	body mass
TGL	triacyglycerol
THR	target heart rate

VO_2max	maximal oxygen consumption
VO_2R	oxygen consumption reserve

10. List of Figures