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Biomolecular Response During Marathon and Ultramarathon Events

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Abstract

The trend of running continues to grow and has even become one of the markers of a modern lifestyle. Many branches of the category of extreme distance and endurance began to be competed in the community. Although it is a simple sport, in the endurance category, there are many aspects that affect the physiological, endurance and performance especially marathon and ultramarathon events. The human body is forcefully exposed to different levels of injury risk depending on the distance and time traveled during a match from physical to gene and DNA levels. This study systematically summarizes the literature that discusses biomolecular responses and mechanisms shown by the body during marathon and ultramarathon events as a process of maintaining homeostasis and body defense mechanisms.

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INTRODUCTION

Running is increasingly in demand by everyone, and the trend continues to increase. This is due to the positive effect of this sport on health and physical strength, and does not require complex equipment, only a proper pair of running shoes and suitable terrain. Though, running consists of various distances, ranging from track running, marathon, and ultramarathon(K. A. Shin et al., 2016). The various running distances have their own impact on the human body, anatomically, psychologically, and physiologically. Although it looks easy, running is an endurance type of sport that involves all parts of the body (total body workout), so it requires the right technique to achieve optimal results (Hoffman, 2016).

Long-distance running types such as marathons and ultramarathons are popular types of physical activity that can increase carbohydrate, fat, and protein metabolism so as to prevent obesity, diabetes, and cardiovascular disease. On the other hand, the high intensity and endurance required for marathons and ultramarathons can trigger myocardial infarction and sudden death(Real et al., 2005). Endurance exercises for a long time such as marathons and ultramarathons will increase oxygen demand more than 10-15 times compared to the demand at rest. The average intensity during classic marathon is 60% of VO2max in non-elite runners, 70-75% in sprinters and 86% for elite athletes. During the ultramarathon, the average intensity is about 50-55% of VO2max (Górecka et al., 2020).

In addition, strenuous physical exercise such as marathons and ultramarathons can result in damage to the muscle fibers as well as an inflammatory reaction. When inflammation occurs, cells turn into a factory of a wide range of inflammatory intermediaries and growth variables which if maintained can interfere with white blood cells and leukocytes. This disturbance in the form of leukocyte migration is primarily determined by the chemotaxis reaction to chemokines that play an important role in the body's defense mechanism (Y. O. Shin & Lee, 2013). Not only does the body's defense system react during marathon and ultramarathon events, but there are also various kinds of biomolecular responses inside these sports. The biomolecular response that occurs can be in the form of an increase or decrease in each of these biomolecular markers. In this paper, we will discuss changes in biomolecular responses during marathon and ultramarathon events.

METHODS

The methodology of this study is literature review or study literature articles from several studies related to biomolecular response during marathon and ultramarathon events. The literature collected from electronic journal databases such as Pubmed, ScienceDirect and Google Scholar. Themes discussed include marathon and ultramarathon trend, acute and chronic injury, fluid and plasma regulations, inflammation, metabolic and cardiac markers fluctuation. The studies were incorporated in this research if they are: 1. in English, 2. mentioned the biomolecular responses during ultra-endurance especially marathon or ultramarathon events, 3. study published not older than 2011, 4. study related to clinical trial, experimental study, systemic review and randomized controlled trial. Studies are not included in the study if there is no relation of biomolecular responses, biomarkers during ultra-endurance events such as in marathons and ultramarathons.

RESULT and DISCUSSION

Ultramarathon Definition and Development

Humans want to push themselves to the maximum limit, both in terms of speed, agility and strength. This condition is evidenced by the existence of the ultramarathon running which has more than doubled the number of participants compared to the past 5 years(Y. O. Shin & Lee, 2013). Ultramarathon is defined as a run that involves a longer distance than the classic distance of 42.195 km. The terrain that is taken is also not only a straight track, but also cross-country such as trail running. Examples of distances that are usually contested in an ultramarathon are 50 km, 80 km, 100 km and the furthest is 300 km as in the Marathon des Sables. Due to the long distance traveled, it is not surprising that a race can take days with immense physical and psychological exhaustion (Hoffman, 2016).

In an ultramarathon event, 80% of the runners are male. Participants were dominated by an average age of 45 years and the fastest runners were usually between 30-49 years old for men, and between 30-54 years for women. Most runners have gone through thorough preparation or conditioning before the race. Ultramarathon participants have a greater history of completing previous marathons than traditional marathon runners. Runners who successfully reach the finish line are known to have 7-13 years of experience in similar running events. The main difference between traditional marathoners and ultramarathons is that they run slower at a slightly lower intensity than marathon runners(Knechtle et al., 2012).

Risk of Injury During Events

Long distance running during extreme conditions certainly has a lot of risk of injury. In a study of the 250 km ultramarathon at the Racing the Planet 4 Desert Series, 396 competing runners were followed prospectively to evaluate overall injury/illness, the type, and diagnosis for all medical related conditions. The result is that 85% of runners require medical treatment. The overall incidence was 3.86 every runner and 65 every run after 1000-hour cumulative. Nearly 95% were insignificant, owing it to disorders related to skin, minor musculoskeletal injuries, and other conditions. Other conditions likely occurred on day one, then musculoskeletal and skin injuries starting from the third and fourth day. A jump in age of 10 years was linked with 0.5 fewer injuries/conditions, and female subjects had 0.16 more medical diseases than male subjects. It can be concluded that ultramarathon injuries are more minor injuries that do not cause long-term disability in trained runners(Krabak et al., 2011).

Correlation between Fluid Regulation and the Aquaporin-1 (AQP1) Gene

During marathon and ultramarathon events, one of the things to pay attention to is fluid regulation. Fluid regulation is very important to maintain body homeostasis and to maintain athlete's performance levels. Fluid regulation is influenced by aquaporins (AQP1), which are known as integral membrane pore proteins or water channels. This channel is encoded on chromosome 7 which influences the regulation of body fluids(Rivera et al., 2020).

One of the AQP1 sequence variants has a strong correlation with marathon running, specifically promoting water flow regulation across cell membranes to maintain fluid balance in cells. Strenuous exercise will disrupt muscle cell homeostasis. If each cell is required to complete optimal reaction during marathon and ultramarathon then it must have adequate access to AQP1. The reason

why it is crucial for cardiorespiratory endurance as it promotes fluid transfer in erythrocytes, endothelium, and lung cells and plays an important role in the transference of bicarbonate, carbon dioxide, ammonium, glycerol, potassium ions, water, nitric oxide, trans-epithelial fluid and kidneys(Rivera et al., 2020).

Adequate balance of body fluids can increase blood flow through the micro vessels which will increase oxygen delivery to loaded muscles. Deficiencies in cellular fluid regulation are likely to impair the capacity and performance levels of marathon and ultramarathon running. Therefore, the well-regulation of water flow is influenced by DNA sequence variations which can be explained in the genotype pervasiveness variance between slow and fast athletes during ultra-events 9.

ANGPTL4 Plasma Importance

Energy sources from fatty acids utilize ultra-endurance exercises such as marathon and ultramarathon. Angiopoietin-like protein 4 (ANGPTL4) is a protein in charge of glucose metabolism and lipid regulation, angiogenesis, energy expenditure, and inflammation. It regulates fat metabolism by liming lipoprotein lipase action and activating lipolysis in fat tissue (Górecka et al., 2020).

A significant increase in ANGPTL4 plasma concentrations was shown when doing marathon and ultramarathon sports. Increased plasma secretion of ANGPTL4 is a mechanism against oxidative stress caused by fatty-acid. Changes in plasma lipids suggest a significant presence of systemic fat provisions supporting the hypothesis about lipid oxidation as the primary energy source throughout submaximal intensity physical movement. The level of fatty acids in plasma increased during ultra-events to maintain blood glucose and glycogen in muscles (Górecka et al., 2020).

ANGPTL4 has also shown a key role in the activation of skeletal muscle of AMP-activated protein kinase (AMPK) from the physical movement. The expression and activity of ANGPTL4 and AMPK in the limbs elevated with running as ANGPTL4 mRNA and protein levels in the gastrocnemius and soleus muscles elevated aftermath. During exercise, AMPK activity in skeletal muscle increases glucose uptake by boosting the type 4 glucose transporter shifting to the plasma membrane. For long-endurance exercise, ANGPTL4 can trigger mitochondrial oxidative phosphorylation and glycolysis through AMPK activation, in which ATP production capacity throughout training increases and positively impacts training tolerance (Chang et al., 2018).

Increased Cardiovascular Markers

Running is synonymous with strenuous cardiovascular activity. Quite a number of cardiovascular events occur after running, regardless of the distance. The important markers are the total concentrations of homocysteine and troponin. The study on 26 runners who ran 30-40 km/week measured the total concentration of homocysteine (tHcy) 24 hours before and after the race. The results showed that the plasma tHcy concentration increased by 20% of the participants showing plasma tHcy concentrations >10 mmol/1 (the limit for ischemic heart disease) while, post-event, 50% had plasma tHcy values > 10 mmol/1. Despite, plasma concentrations of total homocysteine (tHcy) were regulated by different variables such as in men and elders, linked with reduced vitamin B12 serum folate concentrations and mutations of methylenetetrahydrofolate reductase (MTHFR C677T) and cystathionine beta synthase gene, life-long metabolic

conditions and consumption of drugs with phenytoin, cyclosporine, and colestipol as its component(Real et al., 2005).

Troponin levels that are correlated to cardiovascular are troponin I (cTnI). Research during ultramarathon in Leadville, Colorado found that 10 runners who met the sample were measured before and after the race, and 8 of them managed to finish the race. There was an increase in the mean cTnI increasing from 0.001 to 0.047 ng/mL. Post-race sample analysis reported that runners who achieved a faster time had elevated cTnl levels than those who crossed the finish line closer to the 30-hour completion time limit. It was concluded that ultramarathon caused significant changes in cardiac parameters. Ultramarathon intensity and race results may also have an impact on post-race cTnl gains (Khodaee et al., 2015).

Inflammatory Marker Changes

Strenuous exercise such as marathon and ultramarathon will provide a strong stimulus for systemic inflammation. It was associated with increased levels of chemokines and cytokines. In a study conducted on 60 volunteer male marathon runners in a row for 308 km. Samples were collected at 3 different distances for white blood cell and serum concentrations analysis including IL8, IP-10, Regulated upon Activation, and Secreted (RANTES), creatine kinase (CK), C-reactive protein (CRP), and eotaxin. Total leukocytes, neutrophils, and monocytes increased significantly during exercise. However, lymphocytes and eosinophils plummeted drastically during training. Serum levels of the neutrophil chemokine IL-8 peaked at 100 km and are sustained by monocytes. IP-10 chemokine concentrations decreased during the end of exercise. The eosinophil chemokine eotaxin dropped slowly during the event, and there was no difference in the levels of the eosinophil chemokine Regulated upon Activation, Normal T-cell Expressed, and Secreted (RANTES) (Y. O. Shin & Lee, 2013). These observations suggest that prolonged endurance exercise is linked with drastic changes in general inflammation and the leukocyte subset disturbances.

Distance and Intensity Correlation to Metabolic Marker Fluctuation

As a result of the high intensity workload on the body, marathon and ultramarathon exercise also affects overall metabolic markers especially the kidneys and liver. Elevated serum levels of creatinine kinase (CK) and lactate dehydrogenase (LDH) are known for muscle damage and cell necrosis. Pain, weakness and decreased muscle strength throughout intense long-distance movements are the results of the skeletal muscle damage from those activities. The uptake in CK post long-duration exercise is more connected to length of duration than to intensity. Alanine transaminase (ALT) and aspartate aminotransferase (AST) function as markers of liver disease, and the prolonged increase after long-distance running exercises such as marathons and ultramarathons lead to serious liver problems. Particularly, ALT and -GTP are markers of liver injury, the level of which increases after long-distance running(K. A. Shin et al., 2016).

A study involving 15 marathon runners with 3 marathon categories (traditional, 100 km and 308 km marathon), intending to assess markers for skeletal muscle, liver metabolism and kidney function taken from blood samples. Post event, an elevation on creatinine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), and creatinine were noticed compared to before event. CK, LDH, AST levels increased at all running distances. Total protein increased higher at a distance of 100 km compared to 308 km.

Albumin increased in the marathon but decreased at a distance of 308 km. Total and direct bilirubin surged at the distances of 100 km and 308 km, with the highest increase at 308 km. BUN/Cr levels increased at a distance of 100 km compared to the other two distances. The final marker, uric acid, was found to be elevated in marathons, and at 100 km distances compared to 308 km. In conclusion, muscle damage, decreased liver function and hemolysis were increased in the 308 km runner, which was categorized as low-intensity compared to the marathon.

The temporary decrease in kidney function was found to be higher in the 100 km runner, which was categorized as medium-to-high intensity.(K. A. Shin et al., 2016) Bilirubin continued to increase up to 2 days after the race, while alkaline phosphatase decreased in the first two days after. CK, AST and ALT increased immediately after the race and continued to increase significantly until the second day after the race(Kupchak et al., 2014). Elevated CK also correlates with oxidative DNA damage. This type of long-distance running will cause damage to DNA which is assessed in the tail, tail length, and tail moment. Classic marathon has a higher tail moment value compared to a shorter distance (21 km and 10 km). Thus, the increase in oxygen intake and supply to active tissues, resulting in higher levels of reactive oxygen species (ROS). Increased ROS in the vascular system through cell infiltration of injured myofibrils, circulating phagocytes and penetrating into peripheral leukocytes, resulting in modification of nucleic acids after strenuous exercise (Ryu et al., 2016).

There is a risk that can occur to changes in kidney function so that detection steps are also needed. It is hoped that the detection of risk and acute kidney injury can be measured simply through a urine dipstick test in runners. Participants on the Western States Endurance Run in 2011 underwent post-race urine and blood dipstick analysis. Those who were prone to injury criteria had higher creatine kinase concentrations than those who did not. Urinary dipstick testing has successfully identified individuals who meet the prone criteria for acute kidney injury with excellent sensitivity and specificity, so urine dipstick testing is highly recommended to prevent runners at risk of falling in an acute kidney injury (AKI) condition (Hoffman et al., 2013). Thus, a proper screening system should be conducted before ultra-events to minimize damage**.**

CONCLUSION

When we run, many aspects are affected not only from a physical or anatomical perspective, but also from a biomolecular perspective. Aspects that are easily seen and felt are fatigue and muscle damage. Biomarkers that are affected are not only on muscle damage alone, but include genes and DNA level, liver metabolism, liver, fat, ATP system, markers of oxidative stress, fluid and plasma homeostasis. Running distance requires different endurance levels. Thus, it will affect changes in biomarkers in the body especially on extreme terrain, and the person must maintain the same intensity over prolonged time while racing against time. In addition, good diet and fluid management, as well as detecting the risk factors can help speed up recovery and prevent from mild to lethal injury, especially in marathons and ultramarathons.

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