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Effect of Exercise and Muscle Contraction on Insulin Action, Transportation and Sensitivity and Muscle Fibres in type II Diabetes Mellitus

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Abstract This review will critically evaluate the role of exercise in increasing the insulin action, transportation and sensitivity in skeletal muscles. The review will also, try to explore the relationship between the insulin stimulation and glucose transporter type 4 (GLUT-4) protein after the exercise The secondary purpose of this review is to explore whether the exercise induced sensitivity of glucose transport activation is mediated by translocation of greater number of GLUT-4 to the cell surface, and the role of different types of exercise in increasing insulin sensitivity. The review concluded that the stimulation of insulin and exercise is relevant to the physiological developed process of GLUT-4, isoform gene expression is precise and associated with the exercise only. While performing the endurance exercise as well as resistance training we can maintain the muscle bulk and prevent the atrophy in DM. Furthermore, it was proved that the resistance training puts direct effects on the muscles glycogen uptake intracellular and extra cellular signalling pathway and GLUT4, when the subject fed the rich diet of carbohydrate and participates in the exercise. These effects also found in the non-diabetes and healthy subjects.

Keywords Exerciseand Insulin, Muscle Contraction, Insulin Action, Type II Diabetes, Glucose Transporter

1. Introduction

Diabetes Mellitus (DM) causes multiple health complications for including blindness, end stage renal failure, heart disease, as well as of the lower extremity amputation. Studies haveestimated that since 2004 there are around 171 million people diagnosed worldwide with diabetes and the figure will reach 366 million by 2030[1].

There are many risk factors associated with DM such as obesity, lack of exercise, bad eating habits and aging.Family history also contributes in the incidence of DM. Primarily, islets of langerhan in pancreas are the regulator of the glucose and cells in the each islet of langerhan can be categorize into three categories as follows; alpha cells which secrete glycogen in ratio of 25%, beta cell which secretes insulin in ratio of 70% and delta cell which secretes somatostatin about 5% in ratio. Cellular glucose uptake is one of the key functions of insulin and it takes place in skeletal muscle, cardiac muscle and adipose tissue. Complications occur when skeletal muscle and liver becomes unable to retrieve metabolised glucose from the cell[2].

It has been proved that the control of blood glucose concentration is a key factor in the management of DM. Glucose uptake in contracting skeletal muscle increases in response to acute exercise, which ultimately lead to improvement in the insulin sensitivity and modifies gene transcription and protein synthesis[3]. Recruitment of insulin-sensitive glucose transporter 4 (GLUT 4) to the sarcolemma and t-tubules augments the membrane capacity for glucose transport[4]. There are some possible signals discussed, which are involved in triggering the mechanism of GLUT4 translocation during muscle contraction, such as nitric oxide (NO), protein kinase C (PKC), glycogen and AMP-activatedprotein kinase (AMPK)[4]. It has been concluded that during and following contraction of muscles, glycogen manifested as an imperative modulator of signalling events during metabolism of glucose.

Insulin sensitivity increases when the insulin concentratio n decreases in the muscle. Similarly, the insulin response maximizes when the effect of insulin maximize. Increased amount of insulin sensitivity can be achieved after the exercise, which is one of the most significant benefits of exercise[5]. Furthermore, single bout of exercise distinctly increases the whole body glucose disposal[6]. Ultimately,

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the sensitivity of the glucose uptake to insulin increases in the skeletal muscle[7].

2. Muscles Contraction Increases the Glucose Transport and Insulin Sensitivity

Several studies have been undertaken to explore the underlying phenomena regarding contraction of the muscle and its effects on sensitivity of insulin[8]. Holloszy et al,[9] defined insulin in terms of its concentration, which cause 50% of the effect on transportation of glucose. The huge amount of glucose transportation increases the insulin concentration in the blood.

The phenomenon involving the muscle contraction increasing the glucose sensitivity in skeletal muscles was first discovered by Richter et al,[7] who stated that the muscle contraction itself or even by the exercise increases the glucose uptake. They recruited six healthy male students (age range 21-24 years) with the mean age of 22 years. All of the participants were instructed to eat at least 300 grams of carbohydrate before three days of exercise participation. After the exercise, the Teflon catheters were inserted in one femoral artery and bilateral femoral veins. The participants were advised to rest in supine position for four hours at the end of which blood samples were taken for the glucose analysis and a needle biopsy from both the quadriceps muscle was taken.

Three sequential euglycemic glucose insulin clamp procedure (measurement procedure for insulin sensitivity) with the insulin infusion were arranged. Glucose uptake after the insulin infusion found higher in exercised thigh as compared to rested thigh. The lactate release recorded significantly decreased ($p<0.005$) in exercise thigh compared to the rested thigh. Insulin sensitivity increased in exercised muscle because of the conversion of large amount of glucose into glycogen. These results were considered preliminary because of the small number of subjects tested.

Hourmard et al,[10] conducted a trial to explore insulin action in the individuals with risk of cardiovascular disease. All the recruited participants were overweight, obese, living a sedentary life and middle aged. They randomly assigned 154 subjects to three exercising groups and one control group. The exercise protocols were selected with different intensities, volume and duration. First group with 41 participants performed the low volume-moderate intensity exercises; the 30 participants of the second group performed low-volume high intensity exercises, and the 43 participants of third group performed high volume-high intensity exercises. There were 40 participants in the control group. The low-volume moderate intensity and high volume high intensity exercise group performed same amount of exercise in terms of time that is 170 minute per week. The protocol of exercise included jogging, walking, cycling and treadmill. Also, the participants were asked to maintain the baseline body weight by taking the normal daily diet.

Oral glucose tolerance test was performed to check the insulin sensitivity. There was no improvement found in insulin sensitivity in low-volume moderate-intensity group (30 minute walking 3-4 times a week) as well as in low-volume high-intensity group (30-45 minute jogging 3-4 days/week). Measuring the insulin sensitivity by the intravenous glucose tolerance test (IVGTT) in all groups, the high-volume high-intensity and low-volume moderate-intensity group was found to be significantly improved ($p<0.05$) where the exercise duration was 170 minute/week with three to four sessions per week for the both groups. Longer duration of exercise showed significant result with the reduced weight 2kg. The duration of exercise was therefore a key factor which was beneficial for the insulin action during the exercise sessions.

On the other hand, the result was found insignificant in low volume high intensity group and the weight of the subjects was increased 1kg. Our finding indicates that the duration of exercise is one of the primary factors which curb the response of insulin action. Hence, there is possibility that exercise at higher intensity activates AMPK in muscles, which ultimately triggers the GLUT4 to translocate in the contracting muscles[4].

3. Muscles Contraction Translocation of Glucose Transporter 4 Isoform Gene Expression (GLUT4)

One of the important cellular function by which exercise training improves the action of insulin is the concentration of GLUT4 in the muscles[11, 12, 13, 14]. As the insulin stimulated, it is imperative for GLUT4 to translocate to surface of membrane for the transportation of the glucose into the cells. The transportation of the GLUT4 to the surface of membrane then facilitates the transportation of the glucose into the fibres of the muscle[15]. With exercise training, the GLUT4 increases in the skeletal muscles which plays a functional important role in the improving the insulin action. Decreased amounts ofinsulin-stimulated glucose transport into skeletal muscle shows the person suffering from diabetes[16] because of the failure of the blood glucose concentration showing that the skeletal muscle plays a major role to maintain the normal blood glucose concentration. Jessen et al,[17] established that the exercise and insulin stimulation are largely physiological significant stimulators of glucose transport.

Evidence from many researches proved that the physical exercise positively regulates the glucose transport in individuals with type II DM[18]. Jessen et al,[17] indicated (GLUT4) as a main glucose transporters isoform, expressed in skeletal muscles. GLUT4 translocation from inter-cellular to plasma membrane as well as T tubules is a key process by which exercise and insulin augments the transport of glucose. With this understanding, it is presumed that after any single bout of exercise, muscle contraction influences the GLUT4 to move from the locality of intra-cellular to membrane of

the cell, which then makes a strong binding capacity for glucose molecules and absorbing into the cell tissues. GLUT4 translocation from intracellular location was also noted to be present when calcium ion release from sarcroplasmic reticulum during the depolarisation phase.

Many studies carried out to find the role of exercise and its effect on GLUT-4 in diabetes patients[19; 20, 21]. To explore this phenomenon further Kern et al,[19] reported that the GLUT-4 concentration increases with the exercise in middle aged and young subject but not in the older aged because of they are less active to perform the exercise sufficiently. , Cononie et al,[20] recruited participants aged >50 and applied single bout of exercise with 40-60 minute of duration at 70-75% of VO2and found noimprovement in the insulin action after the 15-18 hours of exercise because aging is related with a progressive reduction in insulin action. This reduction was based on age itself and also some of the secondary factors such as increased fat, central adiposity and reduction of physical activity[21].

Based on this finding, Cox et al,[22] conducted a trial to find the effect of exercise on GLUT-4 protein in young participants with age less than 30 years and middle to old participants with age range between 50-70 years. They recruited 9 young and 10 older women and 9 young and 8 older men. Same intensity of exercises was selected for the both groups with 70-75% of maximum oxygen uptake. All participants at the beginning screened for the cardiovascular fitness and body composition. None of them used any medication which could affect insulin action. Pre-training intravenous glucose tolerance test (IVGTT) was recorded for the insulin action and for the measurement of GLUT-4 protein, biopsy of vastuslateralis were taken. Consecutive exercises, one hour per day for 7 days, were performed by all participants.Thereafter, 15-17 hours of the last session of exercise IVGTT was recorded and muscle biopsy were taken. 100mg of vastuslateralis muscle mass was obtained by biopsy for the finding of GLUT-4 protein concentration. The same leg was selected for the biopsy before and after the exercise. The adipose tissues, waist and hip girths were noted to be significantly ($P<0.05$) higher in older patients as compared to the younger subjects. The concentration of GLUT-4 protein was found to be significantly increased ($P<0.05$) in young and older man and women. The increased mean GLUT-4 was 3.1 fold. The findings of the result shows that the skeletal muscle of the older man and women preserve the ability to increase GLUT-4 in response to the exercise. All these findings were based on the relative rather than the absolute exercise stimulus which is important controlling factor of GLUT-4 in skeletal muscle.

Kern et al[19] conducted trials to see weather exercise increases the concentration of GLUT-4 insoleus, gastrocnemius, and extensor digitorumlongus muscles. They recruited the Fischer 344 rat's young (6-8months), middle aged (15-17 months) and old (27-29) for 10-15 weeks of treadmill training. After the training protocol they found a significant increase in the GLUT-4 in young and middle aged rats but not in the old but an increase were found in all soleus, gastronemius and extensor digitorumlongus muscles. On the basis of the result Karen et al[19] and Ezaki et al[23]also conducted a study on the young and older obese rats. The selected protocol was approximately 1km/per day treadmill running for four weeks. The concentration of GLUT4 was measured byimmunoblotting in soleus, plantaris, and red quadriceps in young and aged rats. The old rat's showed significantly ($p<0.05$) increased GLUT-4 in all of the muscles. In addition, the young rat's showed significant increase in GLUT-4 only in plantaris muscles. In old aged obese rats a decrease in body weight was noted, plasma triglyceride levels, and plasma free fatty acid. The main finding of this study was that the exercise training intensity (<75%VO2max) increased protein concentration of GLUT-4 in skeletal muscle with all group young, middle and old age. This increase occurred in spite of the significantly lower absolute workloads of the older participants, as evidenced by heart rate and oxygen consumption responses during exercise.

4. Effects of Resistance Exercise (RE) on GLUT4, ERK1/2 (Extra Cellular) Muscle Glycogen Uptake and Akt (Intra Cellular) Signalling Pathways

In patients with DM, resistance exercise is one of the ways of keeping one-self healthy and maintaining a good structure of the body from atrophy and deconditioning. It is known that with increasing age the peripheral resistance increases the insulin resistance in DM but this insulin resistance was found to decrease after exercise because of the adaptation of resistance mode. As, Castanede et al, [24]mentioned in their study resistance training improveswhole body metabolism of carbohydrate and action of insulin in all ages of man and women because of the findings of increased lean body mass.A similar study on animals performed by Adam et al,[25] where they highlighted resistance training improved the insulin stimulation in skeletal muscle, GLUT4 phosphorylation and Glucose uptake in resistance trained rodent rather than sedentary (controlled) group of rodents.

Two path ways were indicated in recent studies which play imperative role in cellular growth. The cellular growth developed in response to muscle contraction in resistance training. Akt (intracellular) signalling pathways and ERK1/2 regulated kinase. The critical enzyme Akt involved to carrying out many signal pathways also known as protein kinase B (PKB) and this PKB effect on glycogen synthesis activation[26].

The same pathway tested by Creer et al,[27] in skeletal muscle of human, who they recruitedeight subjects for the knee extension exercise all ofwhom were trained cyclist. They gave them a low and high carbohydrate dietfollowing which knee extension exercises were performed with moderate weight. At the end of exercise vastuslateralis

muscle biopsy were taken. The unaffected ERK1/2 was found by glycogen availability in muscle but its phosphorylation was augmented under lower and higher glycogen state after resistance training, that is when a cyclist ate a low and high carbohydrate diet and performed knee extension exercise, the investigators indicated that ERK1/2 phosphorylation effect is for the most part controlled by muscle contraction-mediated stress as opposed by metabolic mechanism. Furthermore, it was indicated that opposite to ERK1/2, Akt phosphorylation was influenced by muscle glycogenavailability and was not related to muscle contraction mediated stress. Other trials performed on the same question endorsed that the high muscle glycogen storage Akt phosphorylation were present after 30 min of resistance exercise[28].

The results from the above stated studies showed that the resistance training increases the Akt pathway phosphorylation and ERK1/2 stimulation when the muscle contracted. These are the key factors which reduce the blood glucose and prevent muscle atrophy in DM.

5. Effectiveness of Continued Existence on Muscles Fibres in Diabetes Patients

Continued exercise training is suggested for patients of DM because it increases the blood flow and glucose control. The increased blood flow and glucose control is essential for the amino acid to be delivered into the skeletal muscles and stimulates the synthesis of protein. Also it is activating the satellite cell and decreases the protein breakdown and maintaining the muscles mass[29]. Researchers conducted several trials on this hypothesis to explore out significant connection among diabetes muscles fibre and endurance exercises.

Sanchez et al,[30] conducted a study; the hypothesis of the trial was to whether or not single-fibre contractile function will be compromised in the inactive diabetic rats and whether endurance exercise will protect the function. They conducted the trial on 28 rats and distributed them into non-diabetic inactive groups and diabetic. Before starting the exercise, they determine the peak force which activates the Ca+, physiological values for the diameter of single fibre, myosin heavy chain (MHC) isoform expression and specific tension.

Moderate speed sixty minutes treadmill training was selected for the exercise trained group. After the 12 weeks of treadmill training, their soleous and extensor digitorumlongus (EDL) were dissected. Throughout this investigation, the blood glucose values were not considerably changed within the group, however, reduced quantity of insulin was required to maintain the glucose level in experimental group. In contrast to this, some other physiological indicator were found significant like cellular atrophy was appear in inactive group whereas no atrophy was noted in the exercised group, which was further apparent in peak force reduction 11% in type II fibres in DM rats. But exhaustingly, soleous expressing type I not affected by diabetes or by the exercise.

Sanchez et al,[30] in their trial noted that there was no atrophy found in type I MHC isoform in the soleus, but on the other hand he also found the diabetes affecting the peak force and diameter of extensor digitorumlongus type II fibres.In regard to this observation, fibres from the soleus muscles in weight bearing animals using constantly which protected them to undergo any atrophy. In contrast, non-weighted contraction was found in EDL muscle while walking,[31] While evaluating these trial, it may be described that endurance exercise is helpful regimen in keeping the bulk of the muscle and properties of contraction unaffected from DM.

6. Conclusions

This article reviewed different studies to find out the positive changes which occurred after exercise in the muscles, which ultimately affected the insulin sensitivity, metabolism and glucose uptake in them. With exercise, the glucose transport pathways was stimulated and increased the muscles glucose,which was associated with the release of Ca from sarcoplasmic reticulum (SR) to the GLUT-4 which in turn activated Ca2+/ calmodium-dependent protein kinase (CaMk) 2, the isoform of CaMK found in skeletal muscle

In this review, we also found that the stimulation of insulin and exercise is relevant to the physiological developed process of GLUT-4, an isoform gene expression and is associated with the exercise only which can help maintain the muscle bulk and prevent the atrophy in DM. We also found that insulin sensitivity improved when applied to long duration exercise the cardiac and obese patients and can be related to age as well as the quality and quantity of the exercise attempted.

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