CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3483696

Available online at: http://www.iajps.com ***Research Article***

ANALYSIS OF EFFECT OF LEVOCARNITINE ON MUSCLE GLYCOGEN CONTENT IN TYPE 2 DIABETES IN PAKISTAN

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Article Received: August 2019 **Accepted:** September 2019 **Published:** October 2019

Abstract:

Introduction: *Type 2 diabetes mellitus (T2DM) is a long term metabolic disorder that leads to various complications resulting in decreasing life expectancy by about 10 years. This condition is associated with a derangement in metabolic flexibility, i.e., a derangement in transition from fatty acid to glucose oxidation in response to insulin.****Objectives:*** *In this study, we have observed the effects of levocarntine in T2DM by estimating the glycogen stores of skeletal muscle.*

Methods: *This descriptive study was conducted in Bahawalpur Victoria hospital during January 2019 to July 2019. The study involved 30 healthy male Spragu. Serum creatine phosphokinase (CPK) levels were measured to exclude any skeletal muscle disorder. Rats were fed high fat diet (2 weeks) followed by intra-peritoneal injection of streptozocin (35 mg/kg). On 21st day, after confirmation of type 2 diabetes by measuring plasma glucose and TG/HDL ratio, rats were divided into 2 equal groups; group I (Diabetic) and group II (Carnitine). Group II was administered l-carnitine (200mg/kg) for 6 days. The extensor digitorum muscle (EDL) of rats of both groups were dissected for estimation of muscle glycogen content. The serum free carnitine (FC) levels were also measured.*

Results*: Carnitine treated rats resulted in increase in skeletal muscle glycogen stores ($p<0.001$). Serum free carnitine levels were also found to be higher in carnitine groups.*

Conclusion*: Levocarnitine increases the glycogen stores in type 2 diabetic rats.*

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Please cite this article in press Muhammad Burhan ulhaq et al., ***Analysis of Effect of Levocarnitine on Muscle Glycogen Content in Type 2 Diabetes In Pakistan.,*** *Indo Am. J. P. Sci, 2019; 06(10).*

INTRODUCTION:

Glucose and lipid metabolism are inter related phenomenons in the human body. The number of people with T2DM is spiking worldwide, thus efficient management is required to improve the quality of life of diabetics. Initial management of T2DM consists of weight reduction, regular exercise and controlled diet. Exercise plays a dominant role in controlling hyperglycemia by way of increase in peripheral insulin sensitivity, strengthening insulin bonding and minimizing obesity [1].

Both glucose and free fatty acids (FFA) are consumed by skeletal muscles as sources of fuel for energy production. During the fasting state, FFAs provide major source of energy production, as skeletal muscle glucose uptake is considerably low. After uptake of glucose, insulin secretion from the beta cells of pancreas is stimulated leading which lowers the rate of lipolysis leading to a reduction in plasma FFA levels. Simultaneously, there is a rise in the rate of glucose oxidation in muscle [2]. This transition from fatty acid oxidation to glucose oxidation is called metabolic flexibility. After transfer of glucose into the muscle cells through of GLUT-4 transporter (glucose transporter 4), it is phosphorylated by hexokinase, and then either oxidized by glycolytic pathway or stored as glycogen. As the insulin levels rise, glycogen synthesis rate also improves, i.e; about 70% of glucose is converted to glycogen [3].

About 90% of total glycolytic flux undergoes glucose oxidation, whereas anaerobic glycolysis accounts for the remaining 10 percent. Pyruvate dehydrogenase, an insulin regulated enzyme, plays indispensible role in glucose oxidation. In T2DM, increased FFA suppresses PDH activity, thereby impairing glucose oxidation. Insulin also activates glycogen synthesis by stimulating a series of phosphorylation-dephosphorylation reactions which result in increased activity of protein phophatase and reduced activity of glycogen synthase kinase [4]. During insulin-stimulated state, skeletal muscle is the major tissue of the body that utilizes glucose; hence it is also a major site of impaired insulin action in T2DM. The combined effect of decreased muscle glucose uptake and the deranged activity of glycogen synthase activity results in about 20% reduction in skeletal muscle glycogen in T2DM, as compared to skeletal muscle of healthy individuals [5].

During exercise, fat oxidation is regulated at the entry of long-chain fatty acid (LCFA) - coenzyme A into the mitochondria of skeletal muscle cell. This entry of LCFA is initiated by transfer of acyl moiety to carnitine (L-3-hydroxy trimethyl aminobutanoate, synthesized from the essential amino acids methionine and lysine). This mechanism is in turn dependant on carnitine palmitoyl transferase 1(CPT-1), which is allosterically inhibited by malonyl-CoA, an intermediate in the synthesis of fatty acids. Thus, this is a likely mechanism by which fat oxidation is suppressed by high glucose availability [6].

OBJECTIVES:

As glycogen is the main source of energy for physical activity and exercise is one of the essential strategies in management of T2DM, the present study was designed to determine the effect of this supplement on skeletal muscle glycogen content in type 2 diabetes.

MATERIAL AND METHODS:

This laboratory based experimental study was conducted Physiology department of Army Medical College, Rawalpindi, in collaboration with NIH, Islamabad. Thirty healthy male Sprague Dawley rats were used. Serum creatine phosphorkinase (CPK) levels were measured to exclude skeletal muscle disorder. The rats were induced type 2 diabetes by administering single dose of streptozotocin (35mg/kg, intraperitoneally), after feeding them 2 weeks high fat diet. A week later, diabetes was confirmed by measuring plasma glucose (>200 mg/dl) and insulin resistance (TG: HDL ratio >1.8) by drawing tail vein blood.[19] Rats were then subjected to 24 hours fast in order to decrease glycogen content. Rats were then divided into two equal groups, group I (Diabetic group) and group II (Carnitine group). Group II rats were administered levo-carnitine for 6 days, at a dose of 200 mg/kg intra-peritoneally. The EDL muscle of all rats was assessed for glycogen content, using an anthrone based method. Serum free carnitine levels of all the rats were measured from terminal intracardiac blood using L-carnitine assay kit.

Data Analysis:

Data was analysed using SPSS 17. Mean and standard deviation were calculated for all values. Statistical significance of difference between the subgroups was determined by applying independent samples t-test. ($p \leq 0.05$ was considered significant).

RESULTS:

The average body weight (174.80 ± 14.42 gm), fasting serum plasma glucose level (97.08 ± 7.19 mg/dl), fasting serum TG (101.38 ± 7.15mg/dl), fasting serum HDL (79.65 ± 5.11mg/dl) and TG:HDL ratio (1.27) in healthy rats were documented initially. After induction of diabetes mellitus, the same parameters were repeated. Statistical analysis showed significant

(p <0.001) increase in weight (268.40 ± 14.65 gm), fasting serum plasma glucose level (404.05 ± 59.65 mg/dl), fasting serum TG (132.17 ± 6.25mg/dl), fasting serum HDL (62.28 ± 1.25mg/dl) and TG:HDL ratio (2.12) due to high fat diet and injection of streptozotocin. [21]

After development of type 2 diabetes, rats were divided into group I and II. Group II rats were administered levo-carnitine for 6 days, at a dose of 200 mg/kg intra-peritoneally. The serum free carnitine was measured by terminal sampling and glycogen content of the EDL muscle of both groups were calculated. An increase in glycogen content was observed in carnitine group II (124.2±17.78 mg/100 gm muscle) as compared to diabetic group I (82.55±10.30 mg/100 gm muscle). The serum free carnitine levels showed a significant rise in carnitine group as compared to diabetic group.

Table 01: Serum free carnitine levels and muscle glycogen content of groups

Variables	Group I (Diabetic) n = 15	Group II (Carnitine) n = 15	Group I v/s II
Carnitine levels (nmol/µl)	0.109 ± 0.014	0.312 ± 0.158	$p < 0.001$
Glycogen content (mg per 100gm muscle)	82.55 ± 10.30	124.20 ± 17.78	$p < 0.001$

All values are expressed as Mean ± SD

DISCUSSION:

Our observation showed that *levo-carnitine* increased the muscle glycogen content in T2DM. The fast twitch muscles (type II) were used because they have comparatively more glycogen stores than the slow twitch muscle. Also, the lower levels of muscle glycogen in T2DM has been observed to be higher in type II muscle fibers as compared to type I muscle fibers. Muscle glycogen is an important fuel for moderate to severe intensity exercise, and exercise is one of the initial regimens for management of T2DM [7]. Studies have shown the that *l*-carnitine increases insulin sensitivity in T2DM, thereby improving glucose uptake by all tissues up to 8% of the basal glucose uptake level [8].

Carnitine has also been shown to improve PDH activity, resulting in reduction of plasma and skeletal muscle lactate levels by improving glucose oxidation [9]. Studies have also proved that increase in plasma carnitine levels results in increased storage of skeletal muscle glycogen. In present study, *l*- carnitine administration has shown to raise the plasma free carnitine levels 3 fold as compared to the diabetic group. Studies by Tamamogullari *et al*. had determined the levels of total, free and esterified carnitines in humans and observed that the levels of these carnitines were decreased in diabetic patients [10]. Free carnitine levels were found to be lower in diabetics while esterified carnitines were found higher in diabetics. L- carnitine supplementation in the carnitine group of our study probably enhanced the PDH activity by buffering the excess acetyl CoA. This was supported by the presence of higher muscle glycogen content after *l*-carnitine administration [11].

CONCLUSION:

Levo carnitine increases the glucose uptake by the skeletal muscle and hence improves the skeletal muscle glycogen stores in type 2 diabetes mellitus.

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