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ORIGINAL ARTICLE

Levocarnitine Supplementation Affects Adiponectin and Serum Lipid Levels in Type 2 Diabetic Mice

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ABSTRACT

Objective: To ascertain the impact of levocarnitine on adiponectin and serum lipid levels in a T2DM mouse model.
Design of the study: Randomized controlled trial
Place and Duration of Study: Department of Physiology, Army Medical College, Rawalpindi from 1stSeptember 2015 to 31stAugust 2017.
Methodology: Forty healthy BALB/c mice, which were allocated to two groups. The mice were initially given a high-fat diet for a fortnight and then induction of T2DM was performed by injecting them with streptozotocin intraperitoneally. Group I was taken as diabetic control, and group II was given levocarnitine. After six additional days, blood samples were analyzed for insulin, adiponectin and lipids.
Results: Adiponectin blood level was significantly increased and an improvement in lipid profile was observed in the levocarnitine group, when compared with control group. In the diabetic control group, a positive significant correlation was observed between (HDL-C) high density lipoprotein levels and adiponectin levels. Additionally, this group also showed total cholesterol and low-density lipoproteins (LDL-C) are negatively proportionate to the adiponectin.
Conclusions: The addition of levocarnitine increases serum adiponectin levels and improves dyslipidaemia in a type of diabetic rats.
Keywords: Adiponectin, Levocarnitine, Lipids

INTRODUCTION

Diabetes mellitus of type 2 (T2DM) is described as a condition resulting from a defective production, action, or both, of insulin which results in hyperglycemia along with disorderly metabolism of carbohydrates, proteins and fats.[1]

Diabetes mellitus of type 2is a major public health concern as it is associated with numerous complications and is showing an alarming upward trend.[2] A primary factor implicated in the aetiology of T2DM is insulin resistance. The inherited polymorphism of the insulin receptor substrate-1 (IRS-1) results in the production of defective insulin which leads to insulin resistance.[3] The main sites of insulin resistance in the body are adipose tissue and skeletal muscles, where fat metabolism is under control of a transcription factor, the peroxisome proliferator-activated receptor-gamma (PPAR-γ).[4]

Adiponectin, an adipokine, is a key player in glucose metabolism and insulin resistance. It performs this function by sensitizing the liver to Insulin and lowering blood glucose levels by inhibiting gluconeogenesis.[5] Adiponectin, in hepatic and skeletal muscle, enhances utilization of glucose and causes oxidation of fatty acids through activation of AMP kinase and acetyl-CoA carboxylase. A deranged lipid profile is considered to be a major contributory factor leading to T2DM.[6]

An organic vitamin, levocarnitine, is made from the amino acids methionine and lysine in the body. It also occurs naturally in meat and dairy products. Levocarnitine is a biologically active form of carnitine and is recognized as a biomarker for testing mitochondrial activity. In mitochondria the transportation of fatty acids for the process of beta-oxidation carnitine is important co-factor.[7]

Impairment of oxidation of fatty acids is observed in carnitine deficiency which results in increased triglyceride levels, elevation of free fatty acids, and excessive build-up of liver fat.[1] Carnitine also performs antioxidant activity, by acting as a scavenger for intracellular superoxide, thus enhances mitochondrial function. Various experimental studies on diabetes have shown carnitine to have a positive effect on functioning of peripheral nerves and diabetic heart, as well as improvement of insulin resistance, and blood flow through vessels. Levocarnitine was also observed to ameliorate fatty liver in mice fed on a high-fat diet and then induced with type-2 diabetic by use of streptozotocin, by increasing fatty acid oxidation and reducing the ratio of levocarnitine/acetyl levocarnitine levels in the liver.[8]

The current research was therefore, planned to assess the impact of levocarnitine on hypoadiponectinemia and dyslipidaemia in type 2 diabetes mellitus.

MATERIALS AND METHODS

The Randomized controlled trial was conducted after receiving approval from the College Ethics Review Committee at the Department of Physiology, Army Medical College Rawalpindi from 1st September 2015 to 31st August 2017. National institute of health sciences provided, twenty healthy (BALB) mice, which were chosen to be aged at 8-12 weeks. Weight of mice was kept 28.07±0.1 gram at an average. The animals were kept in a well-ventilated room with temperature maintained at 20-22°C and at twelve hour cycle of light and darkness. The mice were provided a high-fat diet with water ad libitum for 2 weeks, following which four injections of streptozotocin (STZ) were given intraperitonally in a dose of 40 mg/Kg body weight for four successive days. A high fat diet was continued for all the mice during the 3rd week as well with no additional intervention. At the completion of the fourth week (which was calculated to be 10 days after STZ injections), fasting blood glucose levels were determined to verify the development of a type 2 diabetic model. A blood glucose level of more than 252 mg/dl (14 mmol/l) was considered as the cut off point for confirmation of diabetes. After establishing type 2 diabetes, the mice were then randomly assigned to two groups having 10 mice each; the diabetic control group which was supplemented with regular saline, and the diabetic group supplemented with levocarnitine (200 mg/kg body weight). This intervention was continued for the fifth week and the last blood sample (1.5-2 mls) was obtained by a single intra cardiac puncture at the end of week 5, following an overnight fast. Serum adiponectin, lipid profile, blood glucose levels were all determined according to kit protocol. Data wasanalysed using SPSS-20 and groups were analyzed using one sample t-test, outcome was significant as $p \leq 0.05$.

RESULTS

Adiponectin blood serum reduced in the diabetic control group, but it was significantly ($p<0.001$) increased in levocarnitine

administration groups. The data showed a significant difference (p<0.001) in serum adiponectin levels amongst the groups after the supplementation. Blood adiponectin levels significantly increase d (p<0.001) in the supplementation group when compared to the diabetic control group. Serum total cholesterol (TC), TG, LDL, and VLDL were found to be significantly reduced (p<0.05) whereas serum HDL levels were significantly increased in the supplementation group (Tables 1-2).

Table 1: Adiponectin and lipid values in diabetic control and levocarnitine group

Blood vessels	Control (Type 2 DM)	Drug (Levocarnitine)	P value
Adiponectin (hg/dl)	3.97±0.078	4.42±0.87	<0.001**
Cholesterol (mg/dl)	218.80±30.07	194.70±19.84	0.003**
Triglycerides(mg/dl)	234.90±32.89	156.30±34.74	<0.001**
HDL (mg/dl)	66.28±15.50	89.62±19.57	<0.001**
LDL (mg/dl)	105.55±35.49	69.76±8.62	<0.001**
VLDL (mg/dl)	46.94±6.57	39.90±6.85	<0.001**

P<0.001** (Highly significant)

Table 2: Blood adiponectin Pearson correlation with blood lipids in the control group

Serum adiponectin	r	P value
TC	-0.935	<0.01**
TG	0.666	0.774
HDL-C	0.364	<0.01**
LDL-C	-0.977	0.450
VLDL-C	0.364	0.014*

*0.05 (Significant), **0.01 (Highly significant)

DISCUSSION

In insulin resistance, adiponectin act as a protectant. Adiponectin is inversely proportional to the degree of the obesity. It is the adipose-specific hormone, which is manufactured in white adipose tissue specifically. An association is reported between the degree of insulin resistance with the degree of hypoadiponectinemia, in people with obesity and type 2 diabetes mellitus. We found (3.97 ηg/dl) reduced serum adiponectin, in mice of diabetic control group. Our obtained results are analogous to low adiponectin levels of (2.45 ηg/dl) and (3.35 ηg/dl) in diabetic and obese rates, reported instreptozotocin induced type 2DM by Hashim et al.[10]

Levocarnitine supplements resulted in significant (p<0.001) surge in serum adiponectin. Kubota et al[11] indicated that significant improvement of serum adiponectin levels with pioglitazone along with improvement in insulin resistance and diabetes. Which indicates significance of adiponectin levels with pioglitazone mediated amelioration of hepatic insulin resistance. In July 2021 Tauqir et al[12] reported, daily oral supplement of acetyl Levocarnitine 4mg/kg body weight for 8 weeks can significantly increase serum adiponectin and leptin levels in obese women. Which also improve insulin resistance with an appreciable margin. In the present study, diabetic control mice showed high serum cholesterol, high serum triglycerides, low serum HDL, and high levels of serum LDL and VLDL. In another study Sprague Dawley rats responded with frank hyperglycaemia, raised cholesterol and triglycerides when treated with high fat diet/ streptozotocin.[13] Results of this research found that the adiponectin levels were positively related to HDL values significant, while values of LDL and TC were found negatively related with adiponectin levels. Findings significantly prove the hypothesis that diabetic dyslipidaemia is related with lower adiponectin levels. As indicated in our study, association of adiponectin levels with blood HDL-C and decreased adiponectin can be a stable and useful marker to monitor the dyslipidaemia in females with the polycystic ovarian syndrome (PCOS).[14] On 1st September 2021 Sattarinezhad et al[15] indicated the association of hypoadiponectinemia with dyslipidaemia. Moreover, in uncontrolled type 2 diabetes without or with coronary heart disease, serum adiponectin was negatively associated with fasting glucose levels while HDL-C is positively related with triglyceride level.

Our work indicates, dyslipidaemia can be corrected (p=0.001) significantly by supplementation of levocarnitine, it also increased blood HDL (p=0.001) significantly and reduced TG (p<0.001) again significantly, along with LDL and VLDL in diabetic group. Clinical trials found that levocarnitine attenuates glucose status and lipids levels both when it is used alone or with antidiabetic drugs altogether, L-carnitine promotes sensitivity to insulin along with better lipid levels and enhancing fatty acid consumption in cellular respiration in type 2 diabetes.[16] Mishra and Singh[17] fed L-carnitine to Swiss albino Wistar rats for four weeks (400mg/day) and found increased HDL but markedly improved TG, LDL, and VLDL on oral administration of L-carnitine at double dose.

CONCLUSION

Adiponectin and diabetic dyslipidaemia can be improved significantly with oral levocarnitine, which in turn can increase insulin sensitivity in type 2 diabetes.

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