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Administration of Tadalafil to Patients with Type 2 Diabetes Mellitus and Metabolic Syndrome: A Prospective Randomized Clinical Trial

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Abstract: ***Background: Obesity promotes a state of metabolic syndrome and damages the vascular endothelium by altering lipid profile. Phosphodiesterase-5 (PDE-5) inhibitors restore NO signaling may improve metabolic parameters through a number of mechanisms. We hypothesized that daily administration of the PDE-5 inhibitor; Tadalafil will improve fasting plasma glucose (FPG), triglyceride (TG) levels and body weight, in obese diabetic patients. Methods: Totally, 20 obese diabetic male patients with metabolic syndrome treated with Tadalafil 10 mg daily for 3 months. Body weight, FPG levels, and lipid profile were determined monthly. Results: Treatment with Tadalafil caused a reduction in fasting glucose levels, fasting TGs, cholesterol, low-density lipoprotein (LDL), very-LDL and increased high-density lipoprotein; body weight was significantly reduced. Conclusion: Tadalafil therapy improves glycemic control, lipid profile and body mass index in diabetic patients with metabolic syndrome.***

Keywords: Tadalafil , Obesity, Type 2 diabetes mellitus, Metabolic syndrome

1. Introduction

The incidence of diabetes mellitus associated with obesity was increased highly over the last 30 years especially in those with body mass index (BMI) ≥30 kg/m^2(1).Obesity may lead to secretion of a variety of bioactive substances that might participate in the establishment of insulin resistance (IR) as well as cardiovascular disease (2).The progression of this multifactorial pathology, which targets various tissues and organs, might necessitate a renewal in therapeutic approaches. IR is thought to be an important correlate of other risk factors of the metabolic syndrome such as dyslipidemia and hypertension (3).IR also impacts on lipoprotein metabolism and is associated with an increase in triglycerides (TGs) and depressed high-density lipoprotein (HDL) levels. The ratio of TG-HDL-cholesterol has been widely used as a simple marker to predict the association of patients with IR(4).

Phosphodiesterase-5 (PDE-5) enzymes are found in most vascular beds and by causing their inhibition, nitric oxide (NO•) driven cyclic guanosine-monophosphate breakdown is reduced, resulting in potent vasodilatation. Since cyclic nucleotide PDEs enzymes, which hydrolyze cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), play a crucial role in regulating endocrine and cardiovascular functions, inflammation, oxidative stress, and cell proliferation, all of which contribute to metabolic syndrome(1,3).

Modulation of NO upstream of cGMP has been shown to affect insulin action. Tadalafil , a PDE-5 inhibitor is a vasoactive drug developed for the treatment of erectile-dysfunction also used in the management of pulmonary hypertension and Raynaud's phenomenon(5).

The aim of this study is to investigate the effect of Tadalafil on lipid profile and glycemic control in diabetic patients with metabolic syndrome.

2. Methods

This is a randomized, prospective clinical trial carried out at obesity therapy and research unit, Al-Kindy College of Medicine. Totally, 25 male patients with metabolic syndrome, aged 53.75 ± 6.8 years were randomly assigned. They received 10 mg of Tadalafil once daily for 3 months. The inclusion criteria were patient with of metabolic syndrome which were defined as fasting plasma glucose (FPG) ≥126 mg/dl or 2 hrs plasma glucose ≥200 mg/dl, serum concentration of TG <400 mg/dl, serum cholesterol having 150 mg/dl, <20 mg/dl of HDL, and BMI more than 24. Exclusion criteria were history of myocardial infarction or stroke taking nitrite, insulin therapy, incidence of diseases (such as liver, renal or thyroid disorders), consumption of antioxidant supplements in the past two months, and medications altering cytochrome P450 3A4 (CYP3A4), or history of non arteritic ischemic optic neuropathy. Venous blood samples (10 ml) were collected between 8 and 9 am after fasting for 10-12 hrs. at baseline and after 1 month, 2 months and 3 months of Tadalafil administration. The measurements were performed on frozen serum samples. The serum levels of TG, cholesterol, VLDL, LDL, HDL and fasting glucose were measured using Biotech Engineering Management Co. Ltd. UK apparatus and Croma kit. Glycemic control indices included FPG and hemoglobin A1c (HbA1C). HbA1c was determined using chromatography method by DS5 Drew Scientific machine (ion exchange chromatography). The statistical tests were conducted by paired sample t-test, independent sample t-test, and Ethical approval was obtained from the Medical Ethics Committee of College of Pharmacy, University of Baghdad; the participants signed a written informed consent.

3. Results

The results of this study showed that there is a significant decrease ($p \leq 0.05$) in BMI after 1, 2 and 3 months periods of Tadalafil treatment compared to pre-treatment value (10.9%).The improvement in glycemic control of the studied

patients was seen; fasting blood glucose level decreased significantly after 3 months period by 17.08%; while glycosylated hemoglobin levels decreased significantly after 3 months period by 5.094% compared to the pre-treatment group. Administration of Tadalafil had been result in improvement of lipid profile of the patients, serum level of HDL-C significantly increased by (26.47%) after 3 months treatment with Tadalafil ; total serum cholesterol decreased significantly by (10.85%)after 3 months period compared to pre-treatment value, serum levels of LDL-C was also decreased significantly after 3 months period by 12.47% compared to pre-treatment value. The serum level of TG decreased significantly by 11.24% after 3 months treatment with Tadalafil; indicating the beneficial effect of Tadalafil on lipid profile in these patients (Table 1).

Table 1: Effect of tadalafil administration for three months on glycemic state and lipid profile to diabetic obese patients

Group	*Pre-treatment (n=20)*	*1M*	*2 M*	*3M*	*%change*
BMI (kg/m2)	38.34±6.6	38.22± 6.81*	36.71±6.28*	34.16± 5.69*	10.9
HbA1c	8.008±0.8			7.6±0.7*	5.094
(FSG) (mmol/l)	10.01± 2.5	10.10±2.4	9.5± 2.01	8.3±1.13*	17.08
T.C.	209.5±21.6	203.8±31.09*	192.01±31.2*	186.8± 29.8*	10.85
T.G.	207.4±42.7	199.32±42.4*	192.6± 42.4*	184.08±43.6*	11.24
HDL	35.20±4.9**	37.08±4.95*	40.92± 3.851*	44.520±4.547*	26.47
LDL	117.0±15.2	110.20±14.89	108.0± 16.3*	102.40±15.01*	12.47

Results represent mean±SD; *Significant change where p≤0.05, BMI: Body mass index, FBG: Fasting blood glucose, HbA1c: Glycosylated hemoglobin, S.HDL: Serum high density lipoprotein, S.TC: Serum total cholesterol, S.LDL: Serum low-density lipoprotein, S.VLDL: Serum very low density lipoprotein, S.TG: Serum triglyceride

4. Discussion

According to the results of this study, LDL-C and total cholesterol were significantly lower in post treatment groups. Although LDL-C significantly decreased after 3 months of treatment, there is significantly increased in HDL level and decreased in BMI. The current study is in agreement with results of (7),who showed that chronic inhibition of PDE-5 improves insulin action in a mouse model of diet-induced obesity and one potential mechanism by which PDE-5 inhibition may improve insulin action is prevention of endothelial dysfunction. It has been found that endothelial dysfunction may be causative of IR and Type 2 diabetes (8).Endothelial dysfunction is characterized by a decrease in NO level, reducing cGMP production and impairing muscle glucose uptake(9).Thus, it is possible that preventing a decrease in cGMP levels by inhibiting PDE-5 intervenes downstream of the site of endothelial dysfunction, resulting in improvement. The significant control in the serum lipid levels in treated patients might have been due to the increase insulin sensitivity following Tadalafil administration. There is an evidence that biological responses triggered by oxidative products are associated with lipid peroxidation derivatives, which are able to induce various pathogenic intracellular signals involving calcium, G-proteins, cAMP, cGMP, phospholipase C and D, protein kinase and MAP kinase cascade that leading to cellular dysfunction. Thus increasing cyclic nucleotides by use of PDE inhibitors could overcome to oxidative stress-induced cellular dysfunctions and apoptosis. Supporting this conclusion, Polte and Schroder reported an antioxidant property for NO donors in vascular endothelium through concerted action of cGMP and cAMP. In addition, the hypolipidemic and insulin sensitizing effects of Tadalafil may be attributed to its anti-inflammatory effect(10,11).Anti-inflammatory actions of cGMP signaling in the liver were also shown in a sophisticated study by Tateya et al.(12)who could show that NO/cGMP signaling is down-regulated in mice fed high-fat diet. Concomitantly, inflammation in hepatic Kupffer cells was increased. These effects could be prevented when cGMP breakdown was inhibited by Tadalafil . Recently, it was shown that phosphodiesterase -5- inhibitor promotes browning of white adipocytes *in vitro*(13).Moreover, the importance of PDE-5 for insulin signaling and body weight has been investigated *in vivo*, chronic treatment (12 weeks) with the PDE-5 inhibitor reduced weight gain under high-fat diet. In addition to reduced weight gain, mice showed improved insulin sensitivity. This positive effect of Tadalafil could be due to increased appearance of brown-like adipocytes in white adipose tissue(14).

In conclusion, administration of Tadalafil for three months period improved glycemic control, lipid profile and body mass index in diabetic patients with metabolic syndrome; which may be added as new therapeutic target.

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References

[1] Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med. 2011;9:48.
[2] Matsuzawa Y, Funahashi T, Nakamura T. The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. J Atheroscler Thromb. 2011;18(8):629-39.
[3] Lugnier C. PDE inhibitors: a new approach to treat metabolic syndrome? Curr Opin Pharmacol. 2011;11(6):698-706.

[4] Karelis AD, Pasternyk SM, Messier L, St-Pierre DH, Lavoie JM, Garrel D, et al. Relationship between insulin sensitivity and the triglyceride-HDL-C ratio in overweight and obese postmenopausal women: a MONET study. Appl Physiol Nutr Metab. 2007;32(6):1089-96.
[5] Ho JE, Arora P, Walford GA, Ghorbani A, Guanaga DP, Dhakal BP, et al. Effect of phosphodiesterase inhibition on insulin resistance in obese individuals. J Am Heart Assoc. 2014;3(5):e001001.
[6] Onesi SO, Ignatius UE. Metabolic syndrome: performance of five different diagnostic criterias. Indian J Endocrinol Metab. 2014;18(4):496-501.
[7] Ayala JE, Bracy DP, Julien BM, Rottman JN, Fueger PT, Wasserman DH. Chronic treatment with sildenafil improves energy balance and insulin action in high fat-fed conscious mice. Diabetes. 2007;56(4):1025-33.
[8] Tooke J. The association between insulin resistance and endotheliopathy. Diabetes Obes Metab. 1999;1 Suppl 1:S17-22.
[9] Polte T, Schröder H. Cyclic AMP mediates endothelial protection by nitric oxide. Biochem Biophys Res Commun. 1998;251(2):460-5.
[10] Aboryag NB, Mahmoud AM, Ramadan SA. Sildenafil alleviate insulin sensitivity via attenuating oxidative stress and proinflammatory cytokine production in diabetic rats. Int J Pharm Bio Sci. 2013;4(4):B427-36.
[11] Handa P, Tateya S, Rizzo NO, Cheng AM, Morgan-Stevenson V, Han CY, et al. Reduced vascular nitric oxide-cGMP signaling contributes to adipose tissue inflammation during high-fat feeding. Arterioscler Thromb Vasc Biol. 2011;31(12):2827-35.
[12] Tateya S, Rizzo NO, Handa P, Cheng AM, Morgan-Stevenson V, Daum G, et al. Endothelial NO/cGMP/VASP signaling attenuates Kupffer cell activation and hepatic insulin resistance induced by high-fat feeding. Diabetes. 2011;60(11):2792-801.
[13] Lasar D, Julius A, Fromme T, Klingenspor M. Browning attenuates murine white adipose tissue expansion during postnatal development. Biochim Biophys Acta. 2013;1831(5):960-8.
[14] Mitschke MM, Hoffmann LS, Gnad T, Scholz D, Kruithoff K, Mayer P, et al. Increased cGMP promotes healthy expansion and browning of white adipose tissue. FASEB J. 2013;27(4):1621-30