Low dose tadalafil effect on anthropometric and metabolic parameters in Iraqi diabetic obese men

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ABSTRACT

Background: Phosphodiesterase-5 (PDE-5) inhibitors restore nitric oxide (NO) signaling and may reduce circulating inflammatory markers, and improve metabolic parameters through a number of mechanisms. Daily administration of the PDE-5 inhibitor, tadalafil (TAD) may attenuate inflammation; improve fasting plasma glucose and triglyceride levels and body weight. This study aims to evaluate the efficacy of low dose PDE-5 inhibitor, tadalafil (TAD) in controlling dysglycemia and body weight in obese diabetic men.

Methods: Forty obese men with type 2 diabetes aged 30-50 years incorporated in this study, all with A1c of 7-8.5%, attending obesity unit in AL-Kindy college of medicine. Weight, height, BMI, FPG, A1c, cholesterol, TG, HDL and LDL measured for all and advised for low calories diet and increasing exercise and randomized into 2 groups , first (control) without and the second (therapy) with addition of tadalafil 2.5mg/day for 8 weeks, then remeasure all the parameters after. Results blotted in tables and statistical analysis done using SPSS program and t-test.

Results: There was significant reduction in weight, BMI, FPG, cholesterol, TG and LDL, while no significant change in A1c , and although there was elevation in HDL but was insignificant in control group. In therapy group both weight, BMI, FPG, A1c, cholesterol, TG, and LDL show significant reduction, with mild insignificant elevation in HD. When compare the results of both groups significant results appear in percentage of change of FPG and A1c in therapy group.

Conclusion: Low calories diet and exercise are effective in reducing obesity parameters in type 2 diabetes, in addition, improve dysglycemia and dyslipidemia , adding tadalafil 2.5mg/day can add beneficial effect specifically for FPG and A1c significantly.

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Overweight and obesity represent a rapidly growing threat to the health of populations in an increasing number of countries. Indeed they are now so common that they are replacing more traditional problems such as under nutrition and infectious diseases as the most significant causes of ill-health. Obesity co morbidities include coronary heart disease, hypertension and stroke, certain types of cancer, diabetes mellitus type 2, gallbladder disease, dyslipidemia, osteoarthritis and gout, and pulmonary diseases, including sleep apnea [1]. There is a strong association between obesity and type 2 diabetes. Meta-analysis of studies of association of these two conditions showed higher relative risk with BMI as well as waist circumference in both men and women [2].

Phosphodiestrase enzymes (PDE) activity is found in every cell in the body, although there is distinct cellular and subcellular distribution of the 11 isoenzymes, which has provided many possibilities for increasingly selective therapeutic targets [3]. Tadalafil is a potent, reversible, and selective inhibitor of PDE5, developed as an oral therapy for mild-to-severe erectile dysfunction of psychogenic, organic, or mixed etiology[4] Phosphodiesterase inhibitors (PDIs) have important vascular and myocardial protective effects and have shown therapeutic usefulness in the clinical settings for treatment of patients with heart failure, pulmonary hypertension, and coronary artery disease [5]. Different protocols were designed to test the effect of phosphodiesterase-5 inhibition on insulin action in vivo [6]. PDIs selectively antagonize phosphodiesterase 5(PDE5), which is found in high abundance in a variety of cells potentiate nitric oxide (NO) signaling, chronic treatment with phosphodiesterase-5 inhibitor tadalafil may protect against metabolic stress-induced mitochondrial dysfunction in diabetic hearts [7].

Phosphodiesterase-5 inhibitors restore NO signaling and may reduce circulating inflammatory markers, and improve metabolic parameters through a number of mechanisms. Daily administration of the PDE-5 inhibitor, tadalafil (TAD) will attenuate inflammation, improve fasting plasma glucose and triglyceride levels, body weight, and reduce infarct size after ischemia/reperfusion injury in obese, diabetic mice. Circulating levels of two key pro-inflammatory cytokines, TNF-a and IL-1b were significantly reduced after chronic TAD treatment. There was a trend towards a reduction in IL-6, whereas the anti-inflammatory cytokine IL-10 was significantly higher in TAD treated mice compared to control. With an overall decreased inflammatory profile, improved fasting plasma glucose and triglyceride levels and a trend towards decreased body weight [8].

The study was done with the aim to evaluating the efficacy of low dose PDE-5 inhibitor, Tadalafil (TAD) in controlling dysglycemia and body weight in obese men with diabetes attending obesity research and therapy center, Al-Kindy college of medicine, Iraq.

Methods. A case control comparative study for forty patients, 20 obese diabetics treated with 2.5mg tadalafil (cealis) and 20 diabetics serving as control group.

Inclusion criteria: 1-men aged 30-50 years, had history or presented with type 2 diabetes, according to American diabetes association (ADA) guidelines 2013. Their HbA1c was 7-8.5%. 2-BMI of 30-40 kg/m2

Exclusion criteria: 1-patient with history of or had heart problem (valvular, congenital, ischemic, hypertensive heart failure or cardiomyopathy), 2-any stage of renal or hepatic failure or any other endocrine problem.

Withdrawal Criteria; Development of a hypersensitivity reaction and/or an adverse reaction that necessitated treatment withdrawal, protocol scheduled visits violation or patient's desire to quit.

Site of research: Obesity research and therapy center/AL-Kindy college of medicine, and AL-Kindy teaching hospital from January to June 2014, ethical approval from

scientific and ethical committee of AL-Kindy college college of medicine.

Forty diabetic patients already on diet, exercise and oral antidiabetic drugs randomized into 2 groups, initially all examined for, weight(Wt), height (Ht), body mass index (BMI), fasting plasma glucose (FPG), glycated hemoglobin level (A1c), lipid profile(T.cholestrol, triglycerides (TG), high density(HDL) and low density lipoproteins(LDL). Renal and hepatic function tests, electrocardiogram, chest x ray and echocardiogram if needed to exclude hepatic, renal or cardiac problems. All patients were advised and encouraged to intensify their life style modification to lose weight by low calories diet (reducing their calories intake by 500 Kcal/day) , low saturated fat and moderate intensity aerobic exercise for 45 min daily, to control their glycemia.. A consent form was signed by the patients explaining the procedure and possible drug side effects.

1-group 1; 20 patients maintained on life style medications and their antidiabetic drugs for 8 weeks without any change of drug therapy during. 2-group 2; 20 patients maintained on life style medications and their antidiabetec drugs, and a 2.5 mg tadalafil daily for 8 weeks without any change of therapy during.Patients requested to report for any new symptoms or signs during the research period, after 8 weeks all 40 patients reexamined and investigated as before starting the therapy.

Results expressed as tables and figures , means and percentages blotted, software used is SPSS (MINITAB V16), t- test were used for estimation of P values, P value below 0.05 represent statistical significance.

Results. Only 18 patients of the control group and 17 patients of the tadalafil therapy group completed the 8 weeks due to violation of research methodology (patients did not attend the clinic on time).

Table 1 show the anthropometric (including weight, height, body mass index) , and biochemical (including fasting plasma glucose FPG, glycated hemoglobin HbA1c, total serum cholesterol Ch, serum triglycerides TG, high density lipoprotein HDL, and low density lipoprotein LDL) characteristics of each of control and therapy group and there was no significant statistical differences between both groups, both show high BMI, high FPG, high A1c, elevated cholesterol, triglycerides, LDL, and decrease HDL which is characteristic dyslipidemia associate obesity and diabetes.

Patients in control group had the same instructions of those in therapy group, both advised for low calories diet, decrease saturated fat, increase their exercise to decrease weight, this lead to significant reduction in weight, BMI, FPG, cholesterol, TG and LDL, while no significant change in A1c , and although there was elevation in HDL but was insignificant as it is clear in table 2.

Therapy group response to diet, exercise and tadalafil for 8 weeks is shown in table 3, both weight, BMI, FPG, A1c, cholesterol, TG, and LDL show significant reduction, with mild insignificant elevation in HDL.

To compare the results of the control vise therapy group , percentage of change of each item blotted in table 4 and studied for any significant differences in effect. The results show only significant difference in reduction in FPG and A1c only in favor of therapy group (as illustrated in figure 1 and 2).

Discussion. For long, It had been suggested and proved that obesity has an important causal role in the development of hyperglycemia [9],and hyperlipidemia [10]. Excluding bariatric surgery, low calories diet and exercise had been proven as one of the most effective way to control both weight and glucose level simultaneously (which had strong correlation) in obese type 2 diabetes [11]. Weight loss induced by increased daily physical activity without caloric restriction substantially reduces obesity (particularly abdominal obesity) and insulin resistance in men while exercise without weight loss reduces abdominal fat and prevents further weight gain [12,13].In addition diet and exercise had significant effect on metabolic parameters as plasma glucose, cholesterol level, triglycerides and LDL levels as well even with short term intervention [13], as it is the case in the present study.

This study show insignificant changes in HDL level in response to diet and exercise, other studies may show same result, but intensive lifestyle modification improves the function of HDL even in the face of reduced levels, suggesting increased turnover of proinflammatory HDL [14].

Although diet and exercise alone can cause reduction in

Table 1: Comparison between initial results of control and therapy groups.

Results of initial examination	Control group mean	Control group SD	Therapy group Mean	Therapy group SD	P value
Age (years)	43.00	4.41	41.471	3.04	0.312
Height (cm)	168.78	4.26	170.06	3.07	0.262
Weight (kg)	98.78	8.38	96.65	9.01	0.501
BMI (kg/m2)	34.64	2.125	33.36	2.263	0.093
FPG (mg/dl)	166.72	26.97	172.24	24.18	0.459
A1c (%)	7.753	0.372	7.668	0.385	0.488
Cholesterol (mg/dl)	218.39	41.30	214.53	39.88	0.722
Triglycerides (mg/dl)	188.67	25.28	197.47	26.42	0.379
HDL (mg/dl)	38.22	3.15	39.11	3.74	0.410
LDL (mg/dl)	142.44	39.36	136.29	40.56	0.602

Table 2: Results of Control group initially and after 8 weeks*.

Results of control Group	Control initial mean	Control initial SD	Control After 8 w Mean	Control final SD	Percentage of change
Weight (kg)	98.78	8.38	96.39**	7.78	2.42%
BMI (kg/m2)	34.64	2.125	33.81**	1.91	2.39%
FPG (mg/dl)	166.72	26.97	135.83**	20.08	18.52%
A1c (%)	7.753	0.372	7.688	0.353	0.83%
Cholesterol (mg/dl)	218.39	41.30	205.28**	29.41	6.00%
Triglycerides (mg/dl)	188.67	25.28	170.61**	21.66	9.57%
HDL (mg/dl)	38.22	3.15	39.16	3.05	-2.45%
LDL (mg/dl)	142.44	39.36	132.44**	28.01	7.02%

* After 8 week of intervention(low calories diet and exercise), **P<0.05

Table 3: Results of Therapy group* initially and after 8 weeks.

Results of Therapy group	Therapy initial mean	Therapy initial SD	Therapy After 8 w Mean	Therapy final SD	Percentage of change
Weight (kg)	96.65	9.01	94.00**	8.26	2.74%
BMI (kg/m2)	33.368	2.263	32.455**	2.08	2.73%
FPG (mg/dl)	172.24	24.18	142.47**	18.97	17.28%
A1c (%)	7.668	0.385	7.407**	0.333	3.40%
Cholesterol (mg/dl)	214.53	39.88	198.47**	19.15	7.48%
Triglycerides (mg/dl)	197.47	26.24	169.74**	23.35	14.04%
HDL (mg/dl)	39.11	3.74	40.35	3.70	-3.17%
LDL (mg/dl)	136.29	40.56	124.35**	21.08	8.76%

*Intervention include(diet, exercise and tadalafil), **P<0.05

Table 4: Comparison of percentage of change in control and therapy group.

Parameter	Control group Percentage of change	Therapy group Percentage of change	P values
Weight (kg)	2.45	2.75	0.373
BMI (kg/m2)	2.44	2.78	0.356
FPG (mg/dl)	8.02	21.67*	0.010
A1c (%)	0.85	3.50*	0.001
Cholesterol (mg/dl)	5.95	6.83	0.767
Triglycerides (mg/dl	10.92	16.98	0.079
HDL (mg/dl)	-2.64	-3.47	0.629
LDL (mg/dl)	6.61	7.15	0.873

*P<0.05

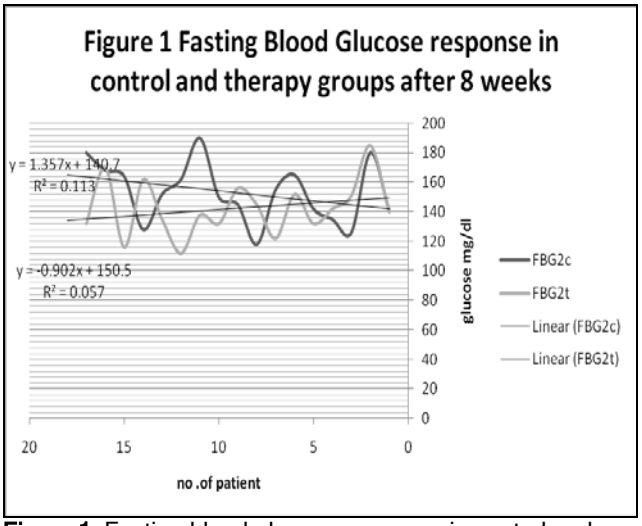

Figure 1: Fasting blood glucose response in control and thearpy groups after 8 weeks.

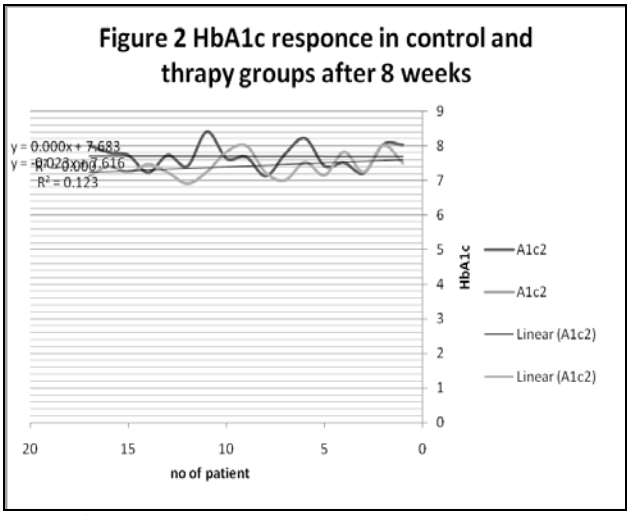

Figure 2: HbA1c responce in control and therapy groups after 8 weeks

A1c level but it was not significant in this study, while many studies show reduction of A1c with diet and exercise [15, 16]. Since one aim of diabetic therapy is to prevent large fluctuations in blood glucose throughout the day, diabetics are advised to select carbohydrate foods that minimize the post-prandial blood glucose excursions[17].

The effect of adding Tadalafil in this study is significant for only FPG and A1c reduction, where reduction of both in taladafil treatment group is more than diet and exercise alone, the possible mechanism is stimulation of nitric oxide-cGMP signaling results in vascular relaxation and increased muscle glucose uptake. It was shown that chronically inhibiting cGMP hydrolysis with the Phosphodiesterase -5 inhibitor improves energy balance and enhances in vivo insulin action [18,19]. Also treatment with tadalafil attenuates oxidative stress and improves mitochondrial integrity while providing powerful cardioprotective effects in type 2 diabetes [20, 21].

Tadalafil treatment with diet and exercise associated with more reduction of weight, BMI, cholesterol, triglycerides and LDL level and elevation of HDL than diet and exercise alone but these changes were insignificant statistically in this study, while other study show significant BMI reduction in men[22]. From studies measuring the respiration rate of brown adipose tissue (BAT), evidence is provided that at concentrations compatible with therapeutic doses, the ability of methylxanthines (PDE inhibitor) to potentiate the thermogenic effect of the sympathomimetic drug, ephedrine, particularly under conditions of caloric restriction, involves a minor contribution of adenosine antagonism, but could mainly be explained by the inhibition of PDE activity, so targeting of PDE activity is therefore a rational approach in the search for drugs that could potentiate sympathomimetic stimulation of metabolic rate [23].

In conclusion, low calories diet and exercise is effective in reducing obesity parameters in type 2 diabetes, in addition improve dysglycemia and dyslipidemia , adding tadalafil 2.5mg/day can add beneficial effect specifically for FPG and A1c significantly.

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