Biochemical changes in overweight and obese patients after taking 5 mg of Tadalafil for two weeks

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Abstract

Background: obesity enhances a chronic inflammation and oxidative stress and damages the vascular endothelium. Tadalafil restores signaling of NO signaling and may decrease circulating oxidative stress and markers of inflammation, and improves parameters of metabolism through a number of mechanisms. The aim of this study to show what the effects of the administration of tadalafil (TAD) on inflammation, and oxidative stress markers in obese male patients.

Methods: 32 male subjects with BMI more than 23 and age range 30-50 years old underwent with TAD 5mg for 14 days .Plasma level of MDA , GsH ,IL-6 and Hs-CRP before the taking of drugs and after 14 days of treatment .

Results: Treatment with TAD caused a non-significant reduction in MDA group (**0.093±0.027 versus 0.082± 0.032, P- value is 0**.196), a non-significant increase in plasma GsH (**0.1074±0.007 versus 0.109±0.009 , p-value is 0**.538), a non-significant of reduction in plasma level of plasma Hs-CRP and IL-6 (**4.377± 0.702 versus 4.272± 0.693, p-value is 0**.599) and (**24.668± 6.001 versus 23.56± 2.587 ,p-value is** 0.401)respectively .

Conclusion: We have concluded that TAD therapy has non –significant effect on anti-inflammatory and anti-oxidant activity if used in short term but this effect may be significant if used for long term or use large dose

Keywords:

1.Introduction

Obesity is a chronic diseases which is cussed by multifactorial which is resulted from many factors such as social, metabolic, psychological, molecular and cellular factors .The World Health Organization define obesity as BMI more than 30 and overweight more than 25 (1).Obesity is an important problem in community . . (2).It has been appeared that low –grade inflammatory process associated with obesity due to presence of white –adipose tissue (WAT) (3).This caused by act by enhancement of immunity which may associate to development of insulin resistance which is characterized by glucose intolerance (3).The result of this process is increasing level of pro-inflammatory markers hormone –like molecules and cytokines (4).This activates of autonomic nervous system in addition to hypothalamic –pituitary –adrenal axis and which lead in glucocorticoids secretions which enhance the development and differentiation of pre-adipocytes and enlargement in(WAT) .This results in more increment of cytokine like Tumour necrosis factors alpha (TNF-α) and IL-6 (5).The increased in circulatory inflammatory mediator causes hypo perfusion in adipose tissue and hypoxia which result in oxidative stress and increased in oxidative stress mediators .(4,5) one of acute –phase protein is C-reactive protein which is produced in the liver that regulate by cytokines like TNF (tumor necrosis factor) , (IL-1)interleukin -1 and interleukin -6 (IL-6) .(2,3,6). Serum levels of high-sensitivity CRP (hs CRP) is more accurate than CRP which can be measured at very low levels by using highly sensitive assays and may be increased in activation of inflammatory in the vessel wall .(6,7,8) . One of the phosphodiesterase -5 (PDE-5) inhibitor is Tadalafil (CialisTM) which have been approved for the treatment of erectile dysfunction (ED) and management of pulmonary arterial hypertension by the (FDA) Food and Drug Administration (9) . The mechanism of action of TAD is increasing the level of cGMP endothelium which triggered by increase the activation of eNOS by chronic administration of PDE-5 inhibitors which has been associated with increased persistent vascular and endothelial function (10,11).One study showed that Chronic administration of TAD in men with ED as an (alternate-day) which appeared efficacy by many mechanism like improved in endothelial function as indicated by marked changes in serum of endothelial function markers , increasing insulin levels and a robust decreasing in the markers of inflammation and high sensitivity C-reactive protein (hsCRP) (12).

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2. Patient and Methods

A randomized study was conducted to evaluate the inflammatory markers and oxidative stress markers for 2-weeks therapy with TAD 5 mg once daily in patients with male patients with overweight and obesity . The protocol of the study was planned and approved by the Ethical Scientific Research Committee in department of Pharmacy ,Bilad Alrafidain University College. From all the participants , informed consent was obtained . The participants of the study of Eligible men were recruited from the outpatient clinic of Diayla government. 32 Men aged 42.63± 6.19 years .All participants involved in this study were had overweight and obesity with BMI more than 23 , with no history of PDE-5 inhibitor use in the last 3 months while The exclusion criteria includes all the following: use NSAIDS, Steroid, nitrate; anti-oxidant agents, history of malignancy, cardiovascular disease high-risk, and kidney failure or chronic liver; in addition to contraindications to TAD. All participants were allowed to take 5 mg daily of TAD with glass water for 2 weeks

Sample collection and preparation

From all participants, two blood samples (10 mL) were collected by venipuncture. The first sample is before taking drugs and the second sample at the end of study. The collected blood samples were put in a heparinized plain tube and centrifuged at 3000 rpm for 10 min and at 4 °C then the plasma obtained was analyzed for biochemical analysis which included:-

1- Evaluate the oxidative stress parameters which include

(a) The plasma malondialdehyde (MDA) level: and it is measurement according to the method which include reaction of thiobarbituric acid (TBA) with MDA which forms TBA2-MDA adducts .This method was called standard method by Stocks and Dormandy (21) and modified by Gilbert et al.;(13).

(b) The plasma level of glutathione (GSH) level: GSH contents (which was measured as total sulphydryl groups) .This is measured according to the method by Godin et al. (14).

2- Measurement of inflammatory parameters by measurement of plasma IL-6 and CRP by using of IL-6 and CRP ELISA-kit .The principle of this method is an in vitro sandwich type assay for the quantitative measurement which depend on on a solid phase enzyme-linked immunosorbent assay.

3. Analysis of Statistics

The results of study which were expressed as mean ± SD; The degree of significant of the Student t-test was used to be a *p* value of less than 0.05.

Results

Effect of TAD on Plasma MDI and GSH.

We evaluate the oxidative stress marker before and after treatment with TAD 5 mg once daily .It appears that there is non-significant changes regarding plasma MDI and GSH as in table 1.

Effect of TAD on Plasma Hs-CRP and IL-6.

We evaluate the anti-inflammatory marker before and after treatment with TAD 5 mg once daily .It appears that there is non-significant changes regarding plasma Hs-CRP and IL-6 as in table 1

Table 1:-Comparative data for pre and post therapy

Variables	Baseline data (Mean ± SD)	After 2 weeks (Mean ± SD)	(95% CI) Baseline *vs* after 2 weeks	*P* value
Plasma MDI(µmol/l)	**0.093±0.027**	**0.082± 0.032**	**(0.0814±0.105) *vs* (0.069±0.095)**	0.196
Plasma GSH(µmol/l)	**0.1074±0.007**	**0.109±0.009**	**(0.104±0.110) vs (0.105± 0.112)**	0.538
Plasma hs-CRP(mg/L)	**4.377± 0.702**	**4.272± 0.693**	**(4.087±4.667) vs (3.986± 4.558)**	0.599
Plasma IL-6 pg/ml	**24.668± 6.001**	**23.56± 2.587**	**(22.191± 27.145) vs (22.492± 24.627**	0.401

4. Discussion

In this study, we showed that the changes in plasma level of Hs-CRP , IL-6 and (MDI and GSH) were non-significant after two weeks of TAD treatment. The causes of non-significant changes may be due to short term use or low dose used. One study showed that sildenafil citrate has the affects to protect against oxidative stress by decreasing the free radical formation and therefore improving antioxidant redox systems.(15,16) .The increasing in lipid peroxidation in overweight and obese patients causes oxidative stress which has the ability to cause various pathogenic intracellular signals including calcium, phospholipase C, cGMP, G-proteins and D, MAP kinase cascade, protein kinase and that made cellular dysfunction. Therefore the use of TAD may overcome the oxidative stress –caused cellular dysfunction and apoptosis by increasing cyclic nucleotide by use of TAD. (17).

In the other hand, there is study showed that TAD has effects to cells of skeletal muscle through improving the capacity of antioxidant in C2C12 cells of skeletal muscle Another study showed that the dose and time of TAD causes different effects on oxidative stress (18). It is found in the other study that the increasing in interval (two tablets with 1.5 days of interval), TAD ingestion had affect to increase in protein carbonylation and malondialdehyde (TBARs). Also there is another study demonstrated that single administration of PDE-5 inhibitors did not induce an increase in oxidation markers. (19) Also there is another study found that IL10 , IL6 and TNF-α were unaffected by the acute TAD administration. In our previous work we have shown that a short term use of TAD did not affect the IL6 level and hs-CRP.(20) In addition to effect of Phosphodiesterase -5-inhibitors on oxidative stress markers ,It found that phosphodiesterase -5-inhibitors have activity against the inflammatory markers .It is found that TAD decreases the plasma level of interleukins and causes normalization the subset of auto reactive T cells in patients with benign prostate hypertrophy .(21) Restoring NO signaling by using of inhibitors of phosphodiesterase-5 (PDE-5) may enhance parameters of metabolism by using many of mechanisms .One of the important mechanisms is as NO donors through activity on cGMP and cAMP.(22

5. Conclusions

Administration of TAD 5 mg for 2 weeks period do not improved oxidative stress markers and inflammatory markers. Further studies are needed to increase the duration and dose

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