DEPLETED LEVELS OF TESTOSTERONE INSTIGATED BY STATINS IN PATIENTS WITH HYPERLIPIDEMIA CAN BE AVOIDED IF SUBSTITUTED BY MORINGA LEAVES

MUNAWAR M[1], ASIF S[1], HABIB H[2], LIAQAT M[2], ALI Y[2], IFTIKLHAR A[2], TARIQ R[1] AND WAQAS M[1*]

1: School of Pharmaceutical Sciences (SPS), Johar Institute of Professional Studies, Lahore

2: Avicenna Medical College

[*]**Corresponding Author: Muhammad Waqas Khan (PhD): E Mail:**

waqaskhanjips@gmail.com; Contact: +923213535005

ABSTRACT

Globallyamong all the factors of death Hyperlipidemia is considered as the mostmomentous one. Therapeutically Statins has been used to control hyperlipidemic crises worldwide at primary and secondary levels. Statins inhibit 3-hydroxy-3methylglutaryl-CoA (HMG-CoA) reductase, anobligatory enzyme for de novo synthesis of cholesterol. Commonly reported unwanted effects of Statins are myopathy, hepatobiliary disorders; rhabdomyolysis, peripheral neuropathy and sexual dysfunctioning. Simvastatin is reported to reduce total testosterone level from 13.4 moll/l to 11.4moll/l and it was also seen that there is a reduced sex hormone binding globulins SHBG value from 35.3 nmol/l to 27.6nmol/l when compared with the subjects who were not treated with simvastatin. The underlying mechanism for reduced testosterone is poor cholesterol availability in lyding cells of testes which use cholesterol for testosterone synthesis. A medicinal plant *Moringa oleifera (M.oleifera)* is commonly known for its reported anti-oxidant, anti-inflammatory, antihyperlipidemic and anti-hypertensive properties. Leaves of *M.oleifera* decrease plasma cholesterol without depleting the testosterone levels. In this comparative cross sectional study 30 male individuals having moderate hyperlipidemia (200-250mg/dl of total

1908

cholesterol level), were selected and divided into three groups (10 each) and given corn starch as placebo to 1st group (G1), 20 mg simvastatin daily to 2nd group (G2) and capsules of 500mg of ground *M. oleifera* leaf powder to 3rd group (G3), for 90 days. 5ml of blood from each member of every group was collected at 0, 15, 30, 45, 60, 75, 90th day. Total serum testosterone was measured by using commercially available testosterone (human) ELISA kit (Abnova- KA0236 Size 96 wells version 02). Analysis of variance ANOVA test were applied in which probability value of $</0.05$ were considered as significance, Results exhibited statistically significant differences ($P \leq 0.05$) among means of G-1and G-2 at15th day and highly significant differences ($P \leq 0.01$) among means of G-1and G-2 at 30th, 75th and 90th day. Our study suggested that *M.oleifera* is better, indigenous and less expensive therapeutic option as compared to statin. It may be used to improve the quality of life in hyperlipidemic patients.

Keywords: HMG-COA reductase inhibitors, Hyperlipidemia, Statins, Testosterone,
Moringa oleifera

INTRODUCTION

Hyperlipidemia is one of the leading causes of mortality worldwide. Several experimental and observational studies establish that inhibitors of 3-hydroxy-3methylglutaryl-CoA (HMG-CoA) i.e. statins reductase cut the death rate in high risk persons with hypercholesterolemia **[1]**. The frequently adverse drug reaction associated with use of statin are myopathy and hepatic dysfunction in addition to these, literature shows that there are lot of evidences of sexual dysfunctionwith use of statins **[2, 3, 4, 5]**. Among Statins simvastatin has supposed to reduce total testosterone level from 13.4 moll/l to 11.4moll/l and it was also seen that there is a reduced sex hormone binding globulins SHBG value from 35.3 nmol/l to 27.6nmol/l when compared with the subjects who were not treated with simvastatin **[6, 7]**. Moreover usage of statins also losses the capacity of testis and is narrates with high hypogonadasim indications and signs resultantly concludes that use of statins is the foremost reason for erectile dysfunction or lessened libido in patients with hyperlipidemia using statins **[8]**. Animal studies have shown that leaves of *M.oleifera* can increase the fecal cholesterol and decrease plasma cholesterol **[9]**. Leaves, roots and flowers of *M. Oleifera* are reported for highly antioxidant properties and are best anti-hyperlipidemic and antioxidant therapy without depleting testosterone levels **[10]**.

MATERIAL AND METHODS

Study design: It was a cross sectional comparative study, **Grouping and treatment:** 30 male individuals having moderate hyperlipidemia (200-250mg/dl of total cholesterol level), were selected for the study and were divided into three groups (10 each) and given corn starch as placebo to 1st group (G1), 20 mg simvastatin daily to 2nd group (G2) and capsules of 500mg of ground *M. oleifera* leaf powder to 3rd group (G3), for 90 days. **Collection and preparation of leaf powder**: *Moringa oleifera* Lam leafs were collected from Botanical garden of Punjab University and were authenticated from botany department of University of the Punjab, Lahore. The leaves were shade dried at room temperature for 2 weeks subsequently grounded into fine powder with the help of grinder. After that the powder were filled in hard gelatin capsules containing 500mg *M. oleifera* powder per capsule. **Collection and storage of blood samples:** 5ml of blood from each member of every group was collected at 0, 15, 30, 45, 60, 75, 90th day. After centrifugation serum was separated and stored in the small eppendorfs and stored at -20°C until they were used for further analysis. **Biochemical analysis:** Total serum testosterone was measured by using commercially available testosterone (human) ELISA kit (Abnova-KA0236 Size 96 wells version 02). **Statistical Analysis:** Data were analyzed by Mean+/- Standard deviation. Analysis of variance ANOVA test were applied in which probability value of $</0.05$ were considered as significant.

Table 1: Showing Groups and daily dose

Total number of groups	Chemicals	Dosing
Group I	Corn starch	500mg twice daily
Group II	*M.oleifera* leaf powder	500mg twice daily
Group III	Simvastatin	20mg once daily

Table 2: Showing the blood sample collection schedule

Total number of collections	Day	Amount of blood taken from each individual
1st collection	Zero	5ml
2nd collection	15	5ml
3rd collection	30	5ml
4th collection	45	5ml
5th collection	60	5ml
6th collection	75	5ml
7th collection	90	5ml

RESULTS AND DISCUSSION

Testosterone in males is synthesized in leydig cells using cholesterol as chief substrate; cells absorb cholesterol from blood via LDL receptors, use of stains clear cholesterol from blood and depriving leyding cells for initiation of de novo synthesis of cholesterol **[11, 12]**. In current study simvastatin was used as standard drug for the treatment of hyperlipidemia at the dose of 20mg daily. Testosterone levels (ng/dl) found at baseline i.e. Day 0 in Group-1, Group-2 and Group-3 were 6.10 ± 1.64, 3.92 ± 0.72 and 10.39 ± 3.17 respectively. (Table 1, Fig 1). One-way Analysis of Variance exhibited that there is non-significant differences between means of G-1, G-2 and G-3. At say 15th the levels of .testosterone were 7.96 ± 1.75, 3.40 ± 0.53, and 10.03 ± 2.70, in G1, G2 and G3 respectively (Table 2, Fig 2). Analysis of Variance exhibited statistically significant differences (P ≤ 0.05) among means of G-2and G-3. (Mean value of testosterone is significantly decreased more in G-2 as compared to G-3). On 30th day the levels of testosterone were 9.87 ± 2.15, 2.67 ± 0.49, and 6.91 ± 1.29 in G1, G2 and G3 respectively (Fig 3), highly significant differences (P ≤ 0.01) among means of G-1and G-2. (Mean value of testosterone is significantly decreased more in G-2 as

compared to G-1). Testosterone levels were 7.50 ± 1.69, 3.24 ± 0.39, and 9.27 ± 2.34 respectively in G1, G2 and G3 at 45th day (Fig 4). One-way Analysis of Variance exhibited statistically significant differences (P ≤ 0.05) among means of G-2and G-3. (mean value of testosterone is significantly decreased more in G-2 as compared to G-3). On 60th day the levels were 7.09 ± 1.28, 3.87 ± 0.77, and 8.82 ± 1.52 respectively (Fig 5). One-way Analysis of Variance exhibited statistically high significant differences (P ≤ 0.01) among means of G-2and G-3. (Mean value of testosterone is significantly decreased more in G-2 as compared to G-3). The levels were found as 7.67 ± 1.38, 3.30 ± 0.35, and 10.03 ± 2.52 respectively on 75th day (Fig 5). One-way Analysis of Variance exhibited statistically high significant differences (P ≤ 0.01) among means of G-2and G-3. (Mean value of testosterone is significantly decreased more in G-2 as compared to G-3). The results showed that Testosterone levels (mg/dl) found at Twelfth week (Day 90) Group-1, Group-2 and Group-3 were 8.44 ± 1.60, 3.26 ± 0.63, and 7.44 ± 1.76 respectively. The results are presented in graphical form (Figure 6, 7). One-way Analysis of Variance exhibited statistically significant differences (P ≤ 0.05) among means of G-1and G-2. (mean value of

testosterone is significantly decreased more in G-2 as compared to G-1). Current study suggested then use of moringa has better

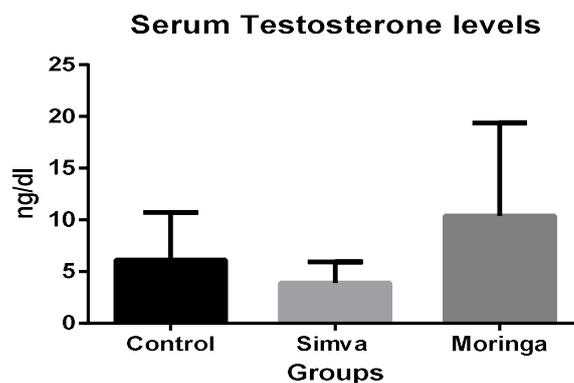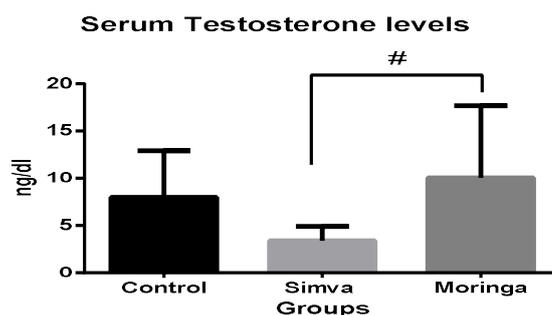Pharmacological and biochemical outcomes as compare to traditional statins.

Serum Testosterone levels
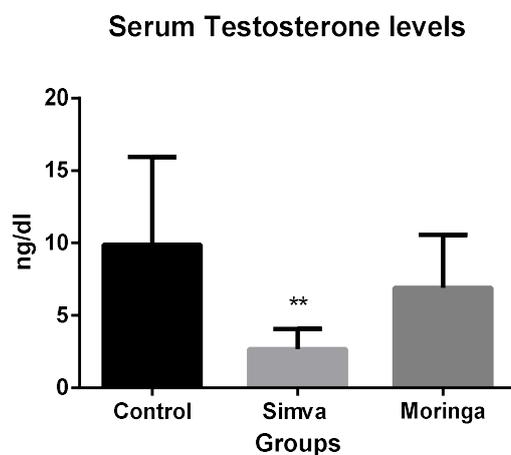

Figure 1

Serum Testosterone levels

Figure 2

Serum Testosterone levels

Figure 3

Serum Testosterone levels

Figure 4

Serum Testosterone levels

Figure 5

Serum Testosterone levels

Figure 6

Serum Testosterone levels
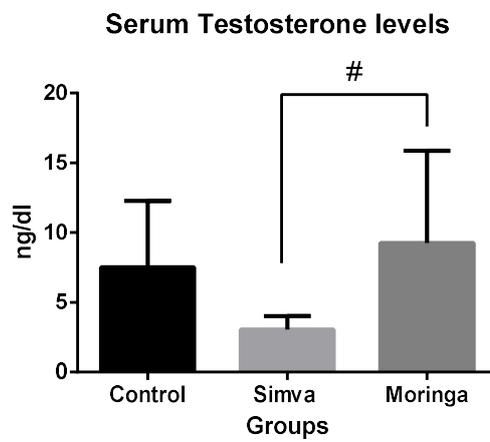
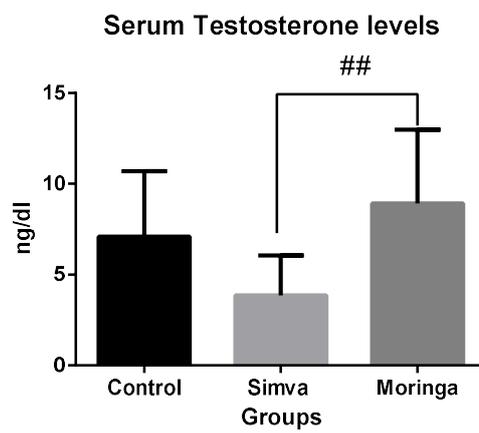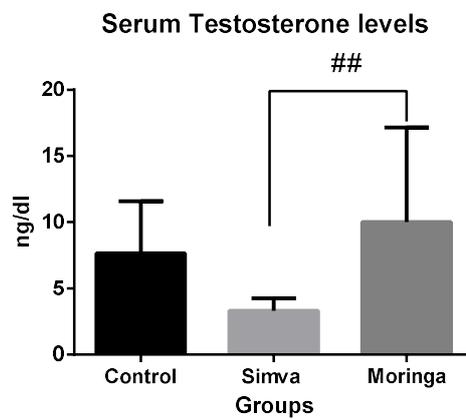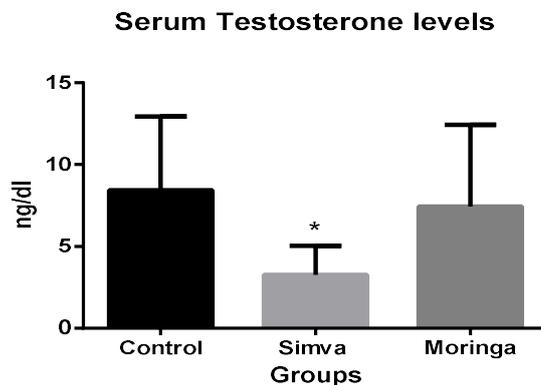**Figure 7**

CONFLICT OF INTREASTS

No conflict of interest were observed

REFERENCES

[1] Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. Journal of the American College of Cardiology. 2004; 43:1405–11.

[2] Smals AG, Weusten JJ, Benraad TJ, Kloppenborg PW. The HMG-CoA reductase inhibitor simvastatin suppresses human testicular testosterone synthesis in vitro by a selective inhibitory effect on 17-ketosteroid-oxidoreductase enzyme activity. The Journal of steroid biochemistry and molecular biology. 1991; 38:465–8. [PubMed: 2031860]

[3] Bruckert E, Giral P, Heshmati HM, Turpin G. Men treated with hypolipidaemic drugs complain more frequently of erectile dysfunction. Journal of clinical pharmacy and therapeutics. 1996; 21:89–94. [PubMed: 8809645]

[4] De Graaf L, Brouwers AH, Diemont WL. Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? British journal of clinical pharmacology. 2004; 58(3):326-8

[5] Rizvi K, Hampson JP, Harvey JN. Do lipid-lowering drugs cause erectile dysfunction? A systematic review. Fam Pract 2002; 19: 95–8.

[6] Jones, P., Kafonek,, S., Laurora, I., and Hunninghake, D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). The American journal of cardiology.1998;5: 582-587.

[7] Antonopoulos, A. S., Margaritis, M., Lee, R., Channon, K. and Antoniades, C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des.2012; 18: 1519-1530.

[8] Corona G, Boddi V, Balercia G, Rastrelli G, De Vita G, Sforza A, Forti G, Mannucci E, and Maggi M. The effect of statin therapy on testosterone levels in subjects consulting for erectile dysfunction. J Sex Med 2010; 7: 1547–1556.

[9] Mehta, K., Balaraman, R., Amin, A. H., Bafna, P. A., and Gulati, O. D. Effect of fruits of *Moringa oleifera* on the lipid profile of normal and hypercholesterolaemic rabbits. J. Ethnopharmacol. 2003; 86, 191–195.

[10] Chumark, P., Khunawat, P., Sanvarinda, Y., Phornchirasilp, S., Morales, N. P., Phivthong-ngam, L & Klai-upsorn, S. P. The in vitro and ex vivo antioxidant properties, hypolipidaemic and anti-atherosclerotic activities of water extract of *Moringa oleifera* Lam. leaves. Journal of ethno-pharmacology, 2008; 116(3), 439-446.

[11] Crenshaw TL, Goldberg PJ. Testosterone in men. In Sexual Pharmacology: drugs that affect sexual functioning. WW Norton &Co., 1996; 115–28.

[12] Griffin JE, Wilson JD. Disorders of the testes. In Harrison's Principles of Internal Medicine, 15th Edn, Braunwald, E, Fauci, AS, Kapser, DL, Hauser, SL, eds Longo DL, Jameson JL. New York: McGraw-Hill Medical Publishing Division, 2001; 2143–54.