Efficacy of Nigella Sativa on Serum Free Testosterone and Metabolic Disturbances in Central Obese Male

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ABSTRACT

Aim: *to study the efficacy of Nigella sativa in central obese men on serum free testosterone, body weight, waist circumference, blood sugar, lipid, uric acid, adiponectin, hs-CRP, and side effects in the treatment group compare to control.*

Methods: *an experimental, clinical test, double blinded with placebo control, pre-test and post-test design. Subjects are 30-45 years old, divided into the treatment and control groups, and evaluated weekly for 3 months. Data obtained were subjective complaints, body weight, waist circumference, and blood pressure, serum free testosterone, fasting blood sugar, triglyceride, HDL-Cholesterol, uric acid, creatinin, SGOT and SGPT, adiponectin, and hs-CRP. Data collected from March 2007 to June 2007 at Prof.Dr.RD Kandou General Hospital, Manado, North Sulawesi, Indonesia. Statistical analysis was performed using descriptive for subjects characteristic and drug's side effect, t independent to compare between two parametric independent variables, Mann-Whitney U to compare between two non-parametric independent variables, and Wilcoxon Signed Ranks test to compare between two non-parametric dependent variables.*

Results: *in the treatment group, complaints related to central obesity disappear in first week, very significant reduction of body weight, waist circumference, and systolic blood pressure, insignificant reduction in serum free testosterone, diastolic blood pressure, fasting blood sugar, triglyceride and cholesterol-HDL, uric acid, hs-CRP, and insignificant increase of adiponectin. On comparison between both groups, we found a very significant reduction on body weight and waist circumference, but the insignificant reduction on serum free testosterone, systolic and diastolic blood pressure, and the unsignificant increase of adiponectin, meanwhile the reduction of serum free testosterone in the treatment group was smaller than the control group, that means Nigella sativa could inhibit the decreasing of serum free testosterone. No side effects were detected in the treatment group.*

Conclusion: *although the other variables in the treatment group were not significantly different, we found them better than the control group, which can be a good sign for metabolic restoration in COM. It is suggested that larger dose and longer duration of NS consumption will give better results.*

Key words: *Nigella sativa, central obese men, serum free testosterone, metabolic disturbances.*

INTRODUCTION

In the last two decades, obesity, especially central obesity in men (COM), has increased worldwide, and already has become a health problem. It is estimated that more than one billion of the world's population is overweight, and at least 300 million of them can be categorized as obese. In some countries, such as China and Japan, the prevalence of population with obesity is 5%. In Indonesia, according to data from Indonesian Ministry of Health, between 1996–1997, there were 17.5% of adults, age between 19–65 years old, who had obesity. In the Minahasa region, North Sulawesi province, the obesity could be found approximately 6.1% in urban region and 7.1% in rural region.[1-3]

Many studies have shown that central obesity has been a risk factor which increases cardiovascular events, related to metabolic syndrome or insulin resistance and other metabolic disturbances. Testosterone hormone, which is identical to human natural testosterone/compounded bio-identical hormone, especially serum free testosterone, has been found to be reduced in COM. The reduction in serum free testosterone is closely related with the increase of body weight, waist circumference, reduction of adiponectin, disturbances of glucose, lipid, uric acid metabolism, also with the increase of the inflammatory

state, marked by the high level of high sensitive-C reactive protein (hs-CRP).[4-6]

Many efforts have been done to reduce COM, in order to restore metabolic disturbances, including using chemical substances, but all of them still can not give a satisfying results. Nowadays, many people are looking for natural source agents to avoid side effects of synthetic chemical substances.[7] *Nigella sativa* is a plant from *Ranunculaceae* family, with 30 – 60 cm in height, larger leaves above, and blue or white flower at the end of the branch which can produce black seeds.[8] The black seed has been already known since a long time ago as spices and medications, especially by the moslems as having medicinal properties. The seeds contain many chemical substances, mainly sterol and essential fatty acids (Ω-3 and Ω-6).[9]

Sterol, which is found in NS, is metabolized in the body, producing testosterone. This testosterone could act like thiazolidinediones, which can activate Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ), then will raise the Glucose Transporter-4 (GLUT-4).[10,11] All the process is suggested to restore the metabolic disturbances, increase adiponectin, and reduce hs-CRP level. Essential fatty acids (Ω-3 and Ω-6) which are anti-inflammatory substances, also have role in reducing Tumor Necrosis Factor-α (TNF-α), interleukin-6, hs-CRP, and in raising adiponectin level.[12,13] Regarding the side effect of NS, it has been shown that the NS seed powder does not produce any toxic effect when given to rabbits by gastric incubation, and another study suggested a wide margin of safety for therapeutic doses of its fixed oil.[14]

The aim of our study was to evaluate, for the first time in humans, the efficacy of NS on serum free testosterone and metabolic disturbances in COM, that were shown by several parameter measurement.

METHODS

This study is an experimental clinical trial, double blinded with placebo controlled, pre-test and post-test design. Subjects are 30-45 year old men from Internal Medicine Policlinic of Prof.Dr.RD Kandou General Hospital Manado who have central obesity according to NCEP-ATP III criteria for Asia – Pacific region (waist circumference ≥90 Cm). The target population were central obese men who fulfilled the inclusion criteria, those who have blood pressure is not exceed hypertension stage I (Joint National Committee VII, 2003), normal or impaired fasting blood sugar (Perkeni, 2006), agreed to participate and sign informed consent. The exclusion criteria were those using drugs, supplement or traditional medicine, drink alcohol during the last 1 month, doing moderate or severe intensity of sports, having liver and or kidney disturbances (creatinin level more than 1.5 mg/dL, liver function (SGOT and or SGPT) three times more than normal, and reverse albumin/globulin ratio, type 2 diabetes mellitus and or gouty arthritis (American Rheumatism Association, 2007), blood pressure more than stage I, refusing informed consent, not following the procedures, and moved out of town or dying during study.

After all the subjects had signed the informed consent, they were randomly divided into treatment and control groups. All subjects in the treatment group had to take two capsules of 750 mg NS twice daily and all the subjects in control group had to take two capsules of 750 mg flour twice daily. They were also allowed to eat normally as they wanted. Initial blood samples were obtained to measure serum free testosterone, fasting blood sugar, triglyceride, HDL-Cholesterol, uric acid, creatinin, albumin/globulin ratio, SGOT and SGPT, adiponectin, and hs-CRP. Both groups were evaluated every week for three months on subjective complaints, body weight, waist circumference, and blood pressure. After three months, the last blood samples were obtained from all subject to measure serum free testosterone, fasting blood sugar, triglyceride, HDL-Cholesterol, uric acid, creatinin, SGOT and SGPT, adiponectin, and hs-CRP.

The data obtained were revealed as texts, tables, and graphs. Statistical analysis was performed using descriptive for subject's characteristics and drug's side effect, t independent to compare between two parametric independent variables, Mann-Whitney U to compare between two non-parametric independent variables, and Wilcoxon Signed Ranks test to compare between two non-parametric dependent variables.

RESULTS

From the data collected between March 2007 and June 2007, 40 subjects were recruited, but there was one subject in the treatment group who dropped out because he moved to other city. At the end of this study, 39 subjects divided into the treatment group and control completed the study for the whole 3 months. Most subjects were 41 to 45 years old. (**Figure 1**)

All subjects reported subjective complaints related to central obesity. (**Table 1**) All subjective complains reported by subjects in the treatment group disappeared in the first week of the study, but they all still persisted in the control group until the end of the study.

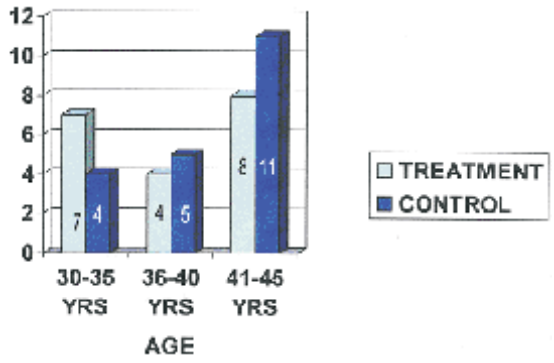

Figure 1. Distribution of subjects according to age

Table 1. Distribution of subjective complains

Complains	Treatment group		Control group	
	Start (%)	End (%)	Start (%)	End (%)
Nausea	4 (21.05)	0	11 (55)	11 (55)
Vomiting	0	0	3 (15)	3 (15)
Belching	3 (15.79)	0	3 (15)	3 (15)
Arthralgia	14 (73.68)	0	18 (90)	18 (90)
Body ache	14 (73,68)	0	16 (80)	18 (90)
Body weakness	12 (63.16)	0	19 (95)	19 (95)
Laziness	14 (73,68)	0	17 (85)	17 (85)
Forgetfullness	17 (89.47)	0	16 (80)	16 (80)
Hair fall	7 (36.84)	0	8 (40)	8 (40)
Aging hair	6 (31,58)	0	10 (50)	10 (50)
Sleepless	11 (57.89)	0	1 (5)	1 (5)
High appetite	14 (73.68)	0	19 (95)	19 (95)
Low libido	16 (84.21)	0	14 (70)	14 (70)

The measurement of serum free testosterone, at the beginning of the study, was revealed in the treatment group, the highest 14.23 pg/mL and the lowest 3.89 pg/mL, with the mean 9.10 ± 2.64 pg/mL. In the control group, the highest 17.06 pg/mL and the lowest 3 pg/mL, with the mean 8.10 ± 3.40 pg/mL. There was no significant difference in this variable. At the end of the study, in the treatment group, the highest 13.81 pg/mL and the lowest 4.44 pg/mL, with the mean 8.95 ± 2.49 pg/mL. In the control group, the highest 14.99 pg/mL and the lowest 1.85 pg/mL, with the mean 7.98 ± 3.13 pg/mL. There was no significant reduction of serum free testosterone in both groups.

The measurement of body weight, at the beginning of the study, in the treatment group, the highest 85 kg and the lowest 68 kg, with the mean 77.11 ± 4.86 kg. In the control group, the highest 100 kg and the lowest 67 kg, with the mean 79.35 ± 8.62 kg. At the end of the study, in the treatment group, the highest 85 kg and the lowest 65.8 kg, with the mean 72.60 ± 5.41 kg. In the control group, the highest 93.5 kg and the lowest 70.3 kg, with the mean 81.14 ± 6.71 kg.

The measurement of waist circumference, at the beginning of the study, revealed in the treatment group, the highest 105 cm and the lowest 100 cm, with the mean 101.2 ± 1.38 cm. In the control group, the highest 105 cm and the lowest 98 cm, with the mean 105.2 ± 5.88 cm. At the end of the study, in the treatment group, the highest 105 cm and the lowest 98 cm, with the mean 99.8 ± 1.78 cm. In the control group, the highest 121 cm and the lowest 100 cm, with the mean 120 ± 66.14 cm.

The measurement of systolic blood pressure, at the beginning of the study, revealed in the treatment group, the highest 150 mmHg and the lowest 100 mmHg, with the mean 130.53 ± 13.11 mmHg. In the control group, the highest 140 mmHg and the lowest 100 mmHg, with the mean 123.50 ± 12.68 mmHg. At the end of the study, in the treatment group, the highest 130 mmHg and the lowest 100 mmHg, with the mean 121.58 ± 7.65 mmHg. In the control group, the highest 140 mmHg and the lowest 100 mmHg, with the mean 126 ± 11.43 mmHg. (**Table 2**)

DISCUSSION

In this study, NS consumption did not significantly raise the serum free testosterone levels and did not significantly restore the metabolic disturbances in COM in the treatment group compare to those in the control group, but from the subjective complaints which disappeared in the first week of the study reduced body weight and waist circumference, and also systolic blood pressure in the treatment group which reduced significantly compared to the control group, we could find possibilities to explain these results. The first, the consumption of NS actually increases the serum free testosterone level, but is mainly used to reduce central obesity, and it is not enough to restore metabolism disturbances in COM.

Secondly, the testosterone which was formed as the result from NS consumption, were bound by the Sex Hormone Binding Globulin (SHBG) into inactive form, and also the newly formed testosterone would rapidly be aromatized into 17β-estradiol and estriol by cytochrome P 450 enzyme and also reduced into dihydrotestosterone by 5α-reductase enzyme. The SHBG and the enzymes are largely produced by adipose tissue in COM.[13]

Thirdly, the dose and the duration of NS consumption were not enough for raising the serum free testosterone level and restoring the metabolic disturbances in COM, although we found that the serum free testosterone level were better and the metabolic disturbances in COM were restored more in treatment than in control group. From data in the

Table 2. Several variable measurement results (mean) in treatment and control groups, before and after treatment

Variables	Treatment Group		Control Group		p (after Rx between both groups)
	Before	After	Before	After	
Serum Free Testosterone (pg/mL)	9.10±2.64	8.95±2.49	8.10±3.40	7.89±3.13	0.292
Body Weight (kg)	77.11±4.86	72.60±5.41*	79.35±8.62	81.14±6.71	0.000
Waist Circumference (cm)	101.2±1.38	99.8±1.78*	105.2±5.88	120±66.14	0.000
Systolic Blood Pressure (mmHg)	130.53±13.11	121.58±7.65*	123.50±12.68	126±11.43	>0.05
Diastolyc Blood Pressure (mmHg)	80.53±13.93	79.47±4.05	80±7.95	82±6.16	>0.05
Fasting Blood Sugar (mg/dL)	95.53±9.30	93.79±8.07	93.25±8.24	92.65±8.31	>0.05
Triglyceride (mg/dL)	202.05±134.31	160.89±88.15	115.05±81.06	150.65±61.44	>0.05
HDL-Cholesterol (mg/dL)	35.60±5.21	34.90±5.20	39.14±7.65	38±8.62	>0.00
Uric Acid (mg/dL)	7.87±1.29	7.54±1.16	8.38±1.74	8.06±1.51	>0.05
Adiponectin (µg/mL)	3.69±1.24	3.89±1.46	3.50±1.37	Med: 3.72	>0.00
Hs-CRP (mg/L)	Med: 1.505	Med:1.795*	Med: 1.595	Med:3.155**	>0.05
SGOT (U/L)	30.15±10.60	25.68±8.37	30.15±10.60	31.70±8.42	>0.05
SGPT (U/L)	49.84±23.90	38.16±19.34	52.85±21.03	46.40±16.91	>0.05
Creatinin (mg/dL)	1.08±0.15	1.02±0.17*	1.06±0.11	1.07±0.12	0.259

*= p< 0.05 in treatment group, **= p<0.05 in control group (un-expected good effect)

treatment group, there were 10 subjects having the serum free testosterone level raised after consumption of NS for three months, and we had already calculated, that the right dose of NS was 40 mg/kg body weight daily for increasing the serum free testosterone level.

Last, we had to consider any effect from the white flour which was given to the control group as placebo or the placebo's effect. The placebo's effect was clearly seen in the adiponectin level, which was raised significantly in the control group, not in the treatment group.

In other variables, compared to the control group, the consumption of NS in the treatment group could slow down the reducing of serum free testosterone, increasing the adiponectin, and reducing of hs-CRP, although there were no significant differences between both groups.

The results of this study are different from the study which was done by Mansi in Jordan, who found a significant increased in serum testosterone levels after consumption of NS in rats.[15] After consumption of NS in rats, the blood sugar and triglyceride level were reduced, and the HDL-Cholesterol levels were increased by Gamze in Turk and Dahri in Saudi.[16,17]

CONCLUSION

The consumption of 3,000 mg of NS daily in COM can significantly reduce body weight, waist circumference, and systolic blood pressure. Although the other variables in the treatment group were not significantly different, we found them better than the control group, which can be a good sign for metabolic restoration in COM. It is suggested that larger dose and longer duration of NS consumption will give better results.

REFERENCES

1. Tambunan V. Overweight and obesity in different ethnic groups in Indonesia. In: Tjokroprawiro A, Soegih R, Soegondo S, dkk, eds. 3rd National Obesity Symposium (NOS III). ISSO. 2004.
2. Ramadhinara A, Widia F, Soegondo S, Setiawati A. The role of SOCS-3 in leptin resistance and obesity. Acta Med Indones. 2008;40(2):89-95.
3. Lukito B. Kadar leptin serum pada suku Minahasa yang obes dan hubungannya dengan resistensi insulin. Karya akhir untuk mencapai gelar dokter spesialis Penyakit Dalam. Bagian Ilmu Penyakit Dalam FK Unsrat Manado. 2003.
4. Rosenbaum M, Leibel RL, Hirsch J. Obesity. N Engl J Med. 1997;337:396-407.
5. Abelson P, Kennedy D. The obesity epidemic. Science. 2004;304:1413.
6. Voya P**.** What every man should know about andropause. California: SpaceAge; 2000. p. 3-4.
7. Black cumin seed oil-backgrounder [cited 2006 December 15]. Available from: URL: http//www.eveone.com.
8. Black seeds. "A cure for every disease except death" [cited 2006 December 15]. Available from: URL: http://www.sweetsunnah.com.
9. Yulianti S, Junaedi E. Sembuhkan penyakit dengan Habbatus Sauda (jintan hitam). 1st edition. Jakarta: Agromedia Pustaka; 2006. p. 14-28.
10. Sacks F, Campos H. Polyunsaturated fatty acids, inflammation, and cardiovascular disease: time to widen our view of the mechanism. JCEM. 2006;91(2):398-400.
11. Werner R. Lipid metabolism. Essential biochemistry and molecular biology. 2nd ed. Connecticcut: Prentice-Hall International;1992. p. 88-114.
12. Holub BJ. Clinical nutrition: Omega-3 fatty acids in cardiovascular care. JAMC. 2002;166(5):608-15.
13. Koolman J, Rohm KH. Biosintesis hormon steroid. In: Sadikin M, eds. Atlas berwarna & teks biokimia. 1st edition. Jakarta: Hipokrates; 2001. p. 328-9.
14. Gargari BP, Attary VE, Rafraf M, Gorbany A. Effect of dietary supplementation with Nigella sativa L. on serum lipid profile, lipid peroxidation and antioxidant defense system in hyperlipidemic rabbits. J Med Plant Res. 2009;3(10):815-21.
15. Mansi KMS. Effects of oral administration of water extract of Nigella sativa on serum concentration in alloxan-induced diabetic rats. Pak J Biol Sci. 2005;8(8):1152-6.
16. Gamze K. Effects of Nigella unguicularis fixed oil on blood biochemistry and oxidant/antioxidant balance in rats. JEP. 2005;99:131-5.
17. Dahri. Effect of Nigella sativa (kalonji) on serum cholesterol of albino rats. J Ayub Med Coll Abbottabad. 2005;17(2):72-4.