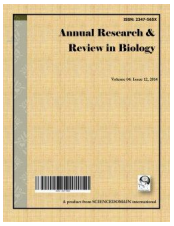

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Oligonol Supplementation Decreases Cardiometabolic Risk Factors, and the Prevalence of Metabolic Syndrome in a Sample of Overweight and Obese Saudi Females

Suhad M. Bahijri[1,2,3*], Anwar Borai[2,4], Zuhier Awan[1,2], Ghada Ajabnoor[1,2,3], Gehan A. Hegazy[1,2,5] and Lubna Alsheikh[2,3]

[1]Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University (KAU), KSA.
[2]Saudi Diabetes Research Group, Faculty of Medicine, King Abdulaziz University (KAU), KSA.
[3]Food, Nutrition and Life Style Research Unit, King Fahd Medical Research Centre, KSA.
[4]Department of Pathology, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Jeddah, KSA.
[5]Department of Medical Biochemistry, National Research Centre, Cairo, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author SMB designed the study, wrote the protocol, supervised recruitment of subjects, sample collection, biochemical analysis and wrote the first draft of the manuscript. Author AB managed the biochemical analyses of the study. Authors ZA and GAH managed the literature searches and helped in writing the first draft. Authors GA, GAH and LA recruited the subjects and managed collection of data. Authors GA and LA performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Cardiovascular diseases (CVDs) are the primary cause of morbidity and mortality worldwide, with metabolic syndrome (MS) increasing their risk. We aimed to investigate the effects of oligonol on cardiometabolic risk factors in healthy overweight and obese Saudi females.

**Corresponding author: E-mail: sbahijri@gmail.com;*

Study Design: A double blind case/control design.
Place and Duration of Study: The study was carried out during December 2015 to June 2016 in the Food, Nutrition and life style research unit, King Fahd Medical Research Centre.
Subjects and Methods: A double blind case/control design was employed. 60 young, apparently healthy overweight and obese females were enrolled, and divided randomly into two groups to take either Oligonol or placebo for 12 weeks without dietary or lifestyle restrictions. Weight, height, waist circumference (WC), and blood pressure were measured and fasting blood samples taken before, and after supplement. Glucose, lipid profile, Apolipoprotein B, Gamma glutamyl transferase (GGT), and highly sensitive C-reactive protein (hs-CRP) were measured, and Atherogenic index of plasma (AIP) calculated in all blood samples. Obtained data was used to diagnose MS.
Results: 25 subjects in placebo group and 22 in Oligonol group completed the study. No adverse effects were noted. Oligonol improved mean triglycerides, AIP, and hs-CRP, and decreased the number of subjects with high triglycerides, diastolic blood pressure, and WC, hence MS.
Conclusion: Oligonol appears to decrease the risk of CVD in obese and overweight Saudi females by controlling or decreasing components of the metabolic syndrome, hs-CRP, and AIP.

Keywords: Cardiovascular disease (CVD); Metabolic syndrome (MS); Atherogenic index of plasma (AIP); Body Mass Index (BMI); High sensitive C-reactive protein (hs-CRP); Apolipoprotein B (ApoB).

1. INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality worldwide, with approximate 17.5 million deaths in 2012, and figures expected to rise if no changes are made to reduce risk factor and increase preventative strategies [1]. The burden of CVD flares within developing countries such as the East Mediterranean region that includes Oman, Kuwait, Saudi Arabia, Lebanon, and Egypt [2,3]. Unfortunately, westernized urbanization known better for its low physical activity and fatty diet, which increase the risk for CVD, has been widely adopted in these countries [2,4,5]. In addition, high rate of consanguinity amplifies the situation by limiting healthy gene diversity [6,7]. Indeed, these factors and changes have increased the prevalence of the metabolic syndrome (MS) in Saudi Arabia [8,9], hence increasing the risk for both diabetes and CVDs further [10]. Recent global multicenter study found that the Saudis have the highest body mass index (BMI) compared to other countries participating in the same study [11].

Thus, there is a major challenge facing these developing countries to reverse or slowdown cardiometabolic risk factors and CVD events in an affordable and cost-effective manner [12].

As such, functional food groups and alternative medicine are being given attention due to low adverse effects, abundant and ease of commercialization [13]. Recently, Oligonol (OLG), a low molecular weight phenolic product derived from lychee fruit extract, is becoming commercially available. It contains catechin-type monomers and oligomers of proanthocyanidins, produced by a manufacturing process converting polyphenol polymers into oligomers [14,15]. Several safety studies have been conducted in humans and animals on OLG. In a single dose toxicity study in rats, OLG (orally 2000 mg/kg body weight /4 weeks) was found to be safe without any adverse events [15]. Furthermore, research studies have also demonstrated; novel antioxidant properties, hypolipidemic activity, anti-inflammatory properties, and ability to modulate the activity of endothelial nitric oxide synthase (eNOS) in endothelial cells in *in vitro* studies [16], all reported to reduce CVD risk.

Various indices have been used for prediction of CVD risk. High-density lipoprotein cholesterol (HDL-C) and triglycerides are the only serum lipids considered as components of MS. However, low-density lipoprotein cholesterol (LDL-C) is the lipid fraction most commonly associated with atherosclerosis [17]. Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL), and an elevation in its level is strongly associated with increased risk of developing CVD [18]. Indeed, it was reported to outperforms LDL-C at predicting risk of coronary heart disease [19,20]. In addition, Atherogenic index of plasma (AIP), a logarithmically transformed ratio of molar concentrations of triglycerides to HDL-cholesterol, has been reported to be a better predictor of CVD risk than the estimation of

serum lipids singly, or total cholesterol/HDL-C ratio, or even apoB. Moreover, various studies reported that increased levels of C-reactive protein (CRP) are associated with the presence of MS [21,22], and increased risk of CVD [23,24]. In addition, recent studies reported that relatively high levels of γ glutamyl transferase (GGT), even if still within the clinically normal range, were associated with increased risk of hypertension, type 2 diabetes mellitus (T2DM), and cardiovascular events, making it an independent risk factor for the development of cardiovascular or cerebrovascular diseases [25-27].

In the present study, we aimed to investigate the effect of OLG supplement on components of MS, and other cardiometabolic risk indicators; namely hs-CRP, GGT, ApoB, and AIP in a sample of overweight and obese Saudi females.

2. MATERIALS AND STUDY DESIGN

2.1 Study Design

The study was designed in a double-blind /Case - Control way. Amino Up Chemical (Sapporo-Japan); as the manufacturers; supplied both Oligonol, and identical placebo capsules, and marked them A and B. Neither the participants nor the researchers were informed which capsules were placebo. After the study was completed, and the data analyzed, Amino Up Chemical identified B as the Oligonol supplement.

2.2 Place and Duration of Study

The study was planned to last 12 weeks, however, due to volunteers starting at different dates, the actual duration was from December 2015 to June 2016.

2.3 Data Description – Volunteers Data

The study was advertised amongst the student population in the medical and health sciences complex at King Abdulaziz University. Apparently healthy Saudi female students, or their friends; aged 20- 34 years; were recruited, and those found to be overweight or obese (Body mass index- BMI > 25 according to WHO classification) were enrolled. Exclusion criteria included those who were suffering from any illness, having a BMI≤ 25, or taking any health supplements regularly.

2.4 Ethical Approval and Informed Consent from All Subjects Included in the Study

The Committee on the Ethics of Human Research at the ‘‘Faculty of Medicine- King Abdulaziz University’’ approved the study, and an informed consent form was signed by all participants. The calculated sample size to detect statistically significant changes in measured parameters was 21 in each arm of the study. Therefore, a total of 60 females were recruited to cover for drop-out from the study.

2.5 Clinical Evaluation of All Volunteers

At base line visit, height was measured to the closest 0.5 cm while bare footed using a stationary stadiometer, and weight was measured while participant was dressed in light clothing to the closest 0.5 kg using a portable calibrated scale (Omron BF511). Body mass index (BMI= kg/m^2) was then calculated using measured height and weight. Waist circumference (WC) was measured between the lowest rib and iliac crest at the level of the umbilicus, to the closest 0.5 cm.

Blood pressure measurement was standardized and carried out using a standard mercury sphygmomanometer with the cuff on the right upper arm, while the subject is sitting comfortably for 10 minutes, according the recommendations of the Joint National Committee [28]. The mean of the two readings, one minute apart, was calculated. A third measurement was taken if a difference > 5 mmHg was found between the two measures and the mean of the two closest readings was calculated. After calculating their BMI, the participants were divided randomly into two equal groups (A and B). A flow chart illustrating the study design, various stages of the study, and the measurements at these stages is presented in Fig. 1.

2.6 Biochemical Assays

Apolipoprotein B (ApoB) was assayed in the clinical chemistry laboratory at King Fahd Armed Forces Hospital- Jeddah, on Siemens BN ProSpec System using nephelometric method. The remaining serum biochemical parameters were assayed in clinical chemistry laboratory at King Abdulaziz Medical City-Jeddah. Both laboratories are fully accredited. Serum glucose, cholesterol, triglycerides, high-density lipoprotein (HDL-C) and gamma glutamyl transferase (GGT)

were assayed on ABBOTT, Architect c8000 auto-analyzer using spectrophotometric method. On the same auto-analyzer, the immunoturbidimetric method was used to measure hs-CRP test. The atherogenic index of plasma (AIP) was calculated using Dobiasova and Frohlich equation [29]. The consensus definition was used to diagnose metabolic syndrome (MS) [30].

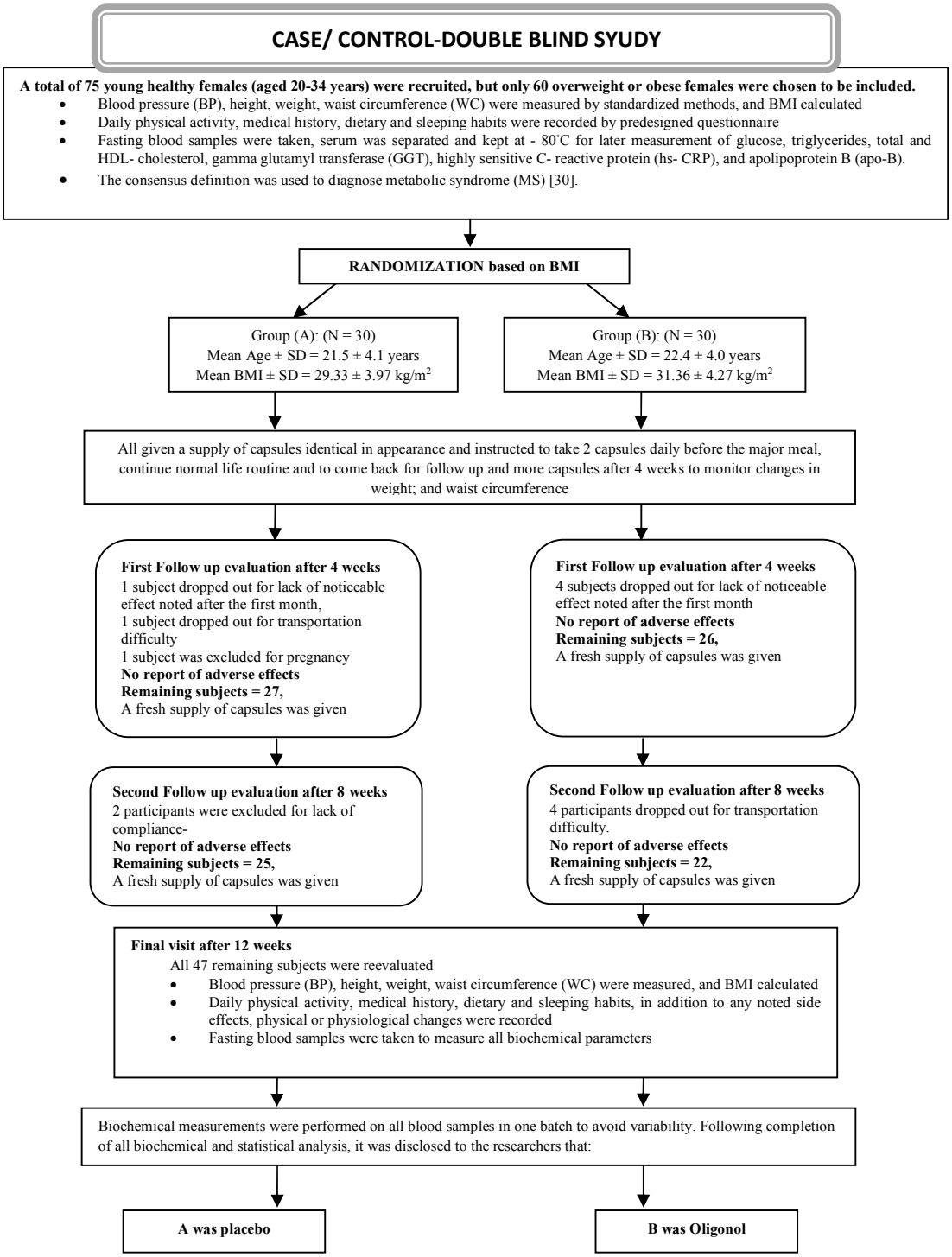

Fig. 1. Summary of study design, various stages of the study, and the measurements at these stages

2.7 Statistical Analysis

Analyses were done by SPSS statistical package version 20.

All measured or calculated parameters are presented as mean ±SD. Means taken at the beginning (pre- supplementation), were compared to corresponding ones at the end of the study (post- supplementation). For normally distributed values, paired Student t-test was used to evaluate differences between means of pre- and post-values for each group, and unpaired t-test to compare means between the two groups. The Mann Whitney-U test was used for comparison of non-normally distributed parameters. In case of waist circumference, which was measured at four occasions, repeated measures ANOVA was used to evaluate variations in means of both groups during the study. Chi square test was used to compare categorical variables. Significance of results was assigned at $p < 0.05$.

3. RESULTS

At the beginning of the study following randomization (Fig. 1), the mean BMI for the two study groups (groups A and B) were not significantly different to each other as stipulated in study design (P= 0.09). Neither was there a significant difference in mean age (P=0.397).

In addition, there was no significant difference between the means of SBP, or DBP of the two groups (P= 0.094 for systolic, and 0,384 for diastolic). Furthermore, there were no statistically significant differences between the two groups in life style habits (P= 0.282 for physical activity, 0.649 for time spent sitting down, 0.442 for sleep duration, 0.613 for usual sleeping time, and 0.659 for smoking).

During the supplementation period of three months, five participants were excluded, or dropped out from group A, and eight from group B, with details outlined in (Fig. 1), and no adverse effects being reported. Therefore, the recalculated mean BMI of group B at the start of the study became (31.63±4.16), and that of group A became (29.30±3.97) hence significantly lower (P= 0.007).

However, no changes were reported during the study in lifestyle habits, and at the end of the study no statistically significant differences between the two groups with respect to reported changes in appetite (P=0.495), gastrointestinal habits (P=0.595), or skin (P=0.797) were found.

Changes in waist circumference (WC) during the whole of the study period are presented in Fig. 2. There was a significant increase in the mean of group A (P= 0.000), compared to a small decrease in-group B (P= 0.058). The change in WC measurements caused the number of subjects with high WC considered to fulfill the criteria of the metabolic syndrome (i.e. > 80 cm) [30] to increase in group A from 14 to 17 females (56% of the group to 68%), compared to a decrease in the numbers (and percentage) in group B from 19 to 16 females (86.4% to 72.7%).

Results of effect of supplementation on components of metabolic syndrome and other cardiometabolic risk factors are presented in Table 1.

Number and percentage of subjects with low value of HDL, high value of TG, FBG, SBP, DBP considered to fulfill the chosen diagnostic criteria of the metabolic syndrome [30], as well as number, and percentage of subjects with MS in group A and group B at the beginning and the end of study are presented in Table 2.

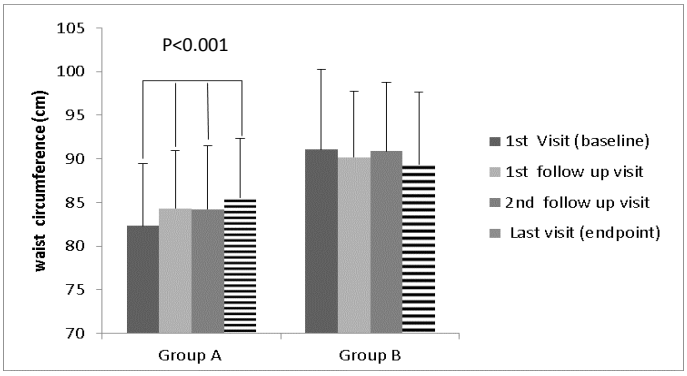

Fig. 2. Changes in waist circumference (WC) during study in groups A & B

Table 1. Components of the metabolic syndrome, and other cardiometabolic risk factors in group A (placebo), and group B (Oligonol) at the beginning and end of the study expressed as mean± SD

Variable	Group A (N=25)			Group B (N=22)			P- value A/B Pre	P- value A/B Post
	Pre	Post	P- value Pre/Post	Pre	Post	P- value Pre/Post		
HDL-C (mmol/L)	1.27±0.19	1.33±0.26	0.157	1.29±0.20	1.22±0.25	**0.030**	0.731	0.158
Triglycerides (mmol/L)	0.74±0.18	0.88±0.3	**0.011**	0.94±0.33	0.78±0.34	**0.008**	**0.017**	0.281
FBG (mmol/L)	4.80±0.37	4.86±0.35	0.390	4.85±0.42	5.09±0.48	0.055	0.722	0.073
SBP (mmHg)	109.8±13.6	107.4±11.0	0.368	115.3±10.1	116.4±8.3	0.704	0.125	**0.003**
DBP(mmHg)	76.7±9.4	71.2±8.5	**0.006**	79.6±9.2	78.0±6.8	0.595	0.292	**0.004**
GGT (U/L)	14.7±5.04	13.7±3.8	0.109	17.2±8.1	15.7±8.7	0.132	0.219	0.334
ApoB (g/L)	0.70±0.13	0.72±0.12	0.454	0.69±0.19	0.65±0.15	0.376	0.972	0.254
PAI	-0.24±0.11	-0.19±0.20	0.126	-0.16±0.18	-0.21±0.18	0.054	0.065	0.685
hs- CRP (mg/L)	3.5±4.5	3.9±5.2	0.212	3.8±4.1	3.6±5.1	0.079	0.492	**0.047**

HDL-C: High-density lipoprotein cholesterol, FBG: Fasting blood glucose, SBP: Systolic blood pressure. DBP: Diastolic blood pressure

Table 2. Number (%) of subjects with low value of HDL, high value of TG, FBG, SBP, DBP considered to fulfill the chosen diagnostic criteria of the metabolic syndrome, and number, and percentage of subjects with MS in group A and group B at the beginning and the end of study

Variable	Group A (N=25)			Group B (N=22)			P- value A/B Pre	P- value A/B Post
	Pre	Post	P- value Pre/Post	Pre	Post	P- value Pre/Post		
No. (%) of subjects with low HDL-C values	12 (48%)	13 (52%)	0.777	11 (50%)	12 (54.5%)	0.763	0.891	0.861
No (%) of subjects with high Triglycerides values	0 (0.0%)	1 (4.0%)	0.312	1 (4.5%)	0 (0.0%)	0.312	0.281	0.343
No. (%) of subjects with high FBG values	2 (8.0%)	2 (8.0%)	1.0	3(13.6%)	3(13.6%)	1.0	0.532	0.532
No. (%) of subjects with high SBP values	2(8.0%)	1(4.0%)	0.552	3(13.6%)	1(4.5%)	0.294	0.532	0.926
No. (%) of subjects with high DBP values	2(8.0%)	1(4.0%)	0.552	8(36.4%)	2(9.1%)	**0.031**	**0.018**	0.394
No. (%)of subjects with metabolic syndrome	2(8.0%)	1(4.0%)	0.552	6(27.3%)	1(4.5%)	**0.039**	0.079	0.926

HDL-C: High-density lipoprotein cholesterol, FBG: Fasting blood glucose, SBP: Systolic blood pressure. DBP: Diastolic blood pressure

Mean HDL-C decreased slightly, but significantly following supplementation with oligonol. However, the number of subjects with lower than acceptable values did not change significantly in either group. On the other hand, following supplementation, mean of triglycerides increased significantly in placebo group, and decreased significantly in Oligonol group. Moreover, the number of subjects with high triglycerides increased in the placebo group, and decreased in the Oligonol group. Similarly, there was a significant decrease in the number of subjects with high DBP in the oligonol group following supplementation. This resulted in a significant decrease in the number of subjects with metabolic syndrome in this group.

There was also some, almost significant, improvement in PAI in the oligonol group (P= 0.054), compared with a slight non-significant deterioration in the placebo group (group A).

Supplementation had no effect on means of GGT, or apoB. However, mean hs-CRP of group B decreased at the end of study, and became significantly lower than that of group A.

4. DISCUSSION

This study aimed to investigate the effect of OLG supplement on various cardiometabolic risk indicators, and components of MS, in overweight and obese females to evaluate its efficacy in combating the rise in the prevalence of CVDs in the kingdom. Our study is the first to investigate these effects in Saudis. An earlier, and smaller Japanese study investigated the effects of OLG on some components of MS in men and women with abdominal obesity, without specifying which criteria were used to diagnose the syndrome, or identifying whether any of the enrolled subjects had MS [31]. In our study, we included females only to avoid gender differences.

Even though all participants were young, and apparently healthy at base line, a considerable percentage (8.0% in-group A, and 27.3% in group B) of them had MS, and were not aware of it. This was mainly due to the criteria used to select the participants (i.e. BMI > 25), hence a high percentage of them had abdominal obesity, considered a component of MS, at the start of the study (56% in-group A, and 86.4% in-group B). Our figures are close to previously reported prevalence rates in Saudis [9]. MS is a reversible condition, which increases the risk for CVDs by two folds [32,33]. Undiagnosed cases will not receive medical advice regarding management of their condition, and thus are likely to develop diabetes and CVD eventually.

Our results indicated that OLG decreased means of three components of MS, namely: triglycerides and DBP significantly (P= 0.008 and 0.031 respectively), and waist circumference slightly (P= 0.058) (Table 1 and Fig. 2). In addition, it decreased the percentage of subjects with high DBP, thus leading to a considerable, and significant decrease in the number of participants with MS from 6 (27.3%) to one (4.5%) (P= 0.039). The Japanese study [31] reported a significant decrease in WC, but no effect on serum lipids in partial agreement with our results. The difference could be attributed to difference in diet between the participants in the two studies, as well as the longer duration of our study, allowing changes in lipid profile to be detected.

In addition to the effects on triglycerides, we noted some beneficial effects of oligonol on Atherogenic index of plasma (AIP). It has been shown that Atherogenic Index of Plasma (AIP) is a strong marker to predict the risk of atherosclerosis and coronary heart disease [34,35]. AIP reflect the true relationship between protective and atherogenic lipoprotein and is associated with the size of pre- and anti-atherogenic lipoprotein particle [29]. However, no effect was noted on mean ApoB, which is an indicator of circulating LDL. The lack of effect could be either a true lack of effect or an undetected one due to use of low dose of OLG, and/or short duration of the study. A study using the dose given in the Japanese study (i.e. 4 instead of 2 capsules/day) might produce different results.

In addition to the favorable effects on the traditional components of MS, OLG supplement was associated with a decrease in mean hs-CRP of group B, making it significantly lower than that of group A at the end of the study. Various studies suggested that the level of hs-CRP is used as a predictor of increased cardiovascular risk, and that it is more indicative than the traditional LDL-C [36]. Furthermore, since it was not found to correlate with LDL-C, it was proposed to be used as an adjunct measurement to the lipid profile to improve risk stratification [36,37]. Thus, OLG appears to act in more than one way to decrease cardiovascular risk.

Oligonol did not also appear to influence mean GGT. Previous studies have indicated that serum GGT can be used as an in vivo biomarker of reduced glutathione (GSH) status [38,39], hence

oxidative stress [40,41]. Therefore, it could be suggested that OLG has no effect on oxidative stress in vivo, unlike to previously reported in vitro effects [16].

The study has some limitations, which are common to this study design, and to working with volunteers. They can be summarized as follows:

The drop out from the study caused the two groups to become dissimilar with respect to mean BMI, even though care was taken to ensure proper randomization and similarity in the beginning. The main reason for dropping out of the study was the high expectations of the subjects who were hoping for quick solution to their weight problems, expecting to lose at least 4 Kg/ month, and when this was not achieved, decided to opt out. The second reason was difficulty in transportation to the study site. Such limitation is common, and quite unavoidable in this type of study when participation is totally voluntary, and no monetary compensation is provided for the participants. To overcome this, paired t- test was used to evaluate changes in means within the same group (pre- versus post-means), and unpaired t-tests were used to evaluate differences in means between the two study groups (pre- A versus pre- B, and post- A versus post-B).

The second limitation was that changes in lifestyle habits, and dietary intake relied on self-reporting by participants, hence might not be very accurate, especially that overweight and obese individuals tend to under-report their dietary intake [42]. However, the participants completing the study were all students from the faculty of medicine, or other health sciences, hence were trained in scientific reporting, and appeared to have done that accurately.

5. CONCLUSION

OLG appears to decrease the risk of CVD in obese and overweight young Saudi females by decreasing hs-CRP, a measure of inflammation, as well as controlling or decreasing some components of the metabolic syndrome, hence decreasing its prevalence. Its use was not associated with any undesirable side effects during the study period. A larger study with a longer duration and an increased dose is recommended to evaluate its future use as an adjunct therapy to lifestyle and behavioral interventions in the hope of combating the rise of CVDs in our region.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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