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# Subject Profile Assessment of Cases Recommended with Nutritional Supplement Containing Red Yeast Rice, Grape Seed Extract and Black Pepper Extract: A Prospective, Multicentric, Post-marketing Study

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## Abstract

**Objective:** To assess the profile and general health indices in subjects prescribed with a nutritional supplement containing red yeast rice, grape seed extract and black pepper extract (NS-YGP; PreLipid®; Abbott Healthcare Pvt. Ltd.) in routine clinical setting in India.

**Methods:** In this prospective, postmarketing observational study, consecutive subjects recommended NS-YG at their outpatient department were recruited from 39 sites in India. The primary outcome of interest was to identify the profiles of subjects recommended with NS-YGP. The secondary outcome measures were to evaluate the changes in lipid profile from baseline to 3 and 6 months and assess the safety of NS-YGP.

**Results:** A total of 573 subjects were enrolled, of which 527 (92%) completed the study. Majority of subjects receiving NS-YGP were males (76.6%), non-obese (85.9%) and had borderline dyslipidemia (87.3%) at the time of enrolment. There was a significant improvement in lipid profile over a period of 6 months; with a significant decline in the levels of total cholesterol, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides from baseline to month 3 and 6 ($p < 0.0001$ for each parameters). Furthermore, HDL-C level significantly improved from baseline till month 6 ($p = 0.0007$). There was a significant change in levels of other laboratory parameters, including creatine phosphokinase, serum creatinine, hemoglobin and white blood cells from baseline to 3 and 6 months ($p<0.05$). No adverse events were reported in the study.

**Conclusion:** Most of the subjects prescribed with NS-YG had borderline elevated lipid levels. NS-YGP significantly improved lipid profile and was safe, well-tolerated and can be recommended in the primordial prevention of borderline dyslipidemia.


## Introduction

Globalization and changing lifestyle, including cumulative behavioral, biological, and social risks have increased the risk of cardiovascular disease (CVD) worldwide.[1] In 2015, mortality attributable to CVD appeared to be the highest representing 31% of all global deaths.[2] Dyslipidemia is an important CV risk factor and has a strong pathophysiological association with progression of coronary atherosclerosis and their clinical sequelae.[2]

Both primary and secondary (concerted and combined) prevention efforts with an early intervention help to reduce the lifestyle disorders like CVD in middle-aged subjects and beyond. Statins, a class of lipid-lowering drugs, are well-known to reduce cardiovascular morbidity and mortality and are often prescribed in advanced stages of CVD.[3,4] But their long-term use has been associated with a risk of adverse events like myalgia, muscle weakness, reduced energy, elevation of liver enzymes, and diabetes.[5] Primordial prevention, through maintenance or adoption of a healthy lifestyle decreases CV risk and, consequently, reduce the incidence of dyslipidemia. Furthermore, it could substantially reduce the economic burden and may be a more feasible target before the development of adverse risk factor profiles in an individual suffering from dyslipidemia.[6]

Over the recent years, there has been a strong shift to traditional healthcare systems like Ayurveda, Unani, herbal and Chinese medicine to treat borderline hyperlipidemia due to better tolerability and effectiveness.[7] This eventually prevent or delays the progression of CVD.[8,9] PreLipid® capsules (abbreviated as NS-YGP; Abbott Healthcare Pvt Ltd) are available as a nutraceutical and is a recommended health supplement for maintaining healthy cholesterol levels. It contains a combination of bioactive molecules from standardized plant extracts (red yeast rice, grape seed extract and black pepper extract), folic acid and vitamin B3 (niacinamide). However, its role has not been fully evaluated and justified in literature. Hence, the present study was sought to determine the profile of subjects who had been recommended NS-YGP. In addition, the effects of NS-YGP on change in different lipid parameters from baseline to 6 months was also explored.

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**Fig. 1: Site distribution**

## Subject and Methods

### Study design and participants

This was a prospective post marketing multi-centric study conducted at 39 clinical sites across India (Figure 1). Subjects with age of 18 years or above who attended the outpatient department at the study sites and recommended NS-YGP by their physician or already on NS-YGP before enrolment were eligible to participate in the study. Subjects with known hypersensitivity to any of the ingredients of NS-YGP or had participated in any clinical study within 3 months before enrolment or had already been diagnosed with any major illness due to which NS-YGP cannot be recommended, were excluded. Pregnant or lactating women were also excluded from the study. Written informed consent was obtained from each subject prior to enrolment. The first subject first visit was on 30 June 2016 and the last subject last visit was on 10 October 2017.

The study protocol and other study-related documents were approved by the independent ethics committees. The study was conducted in full conformity with the principles of the Declaration of Helsinki, International Council for Harmonization-Good Clinical Practices guidelines, Indian Council of Medical Research, Indian GCP guidelines, and as per the approved protocol.

### Study procedures

After enrolment, each subject was assigned a unique subject identification number and was followed, as per their routine visits, at 3 months (± 7 days) and 6 months (± 14 days). The data related to their demographics, past family and medical history, comorbidities, body weight, body mass index (BMI), vital signs (pulse rate and blood pressure), laboratory parameters (lipid profile, blood glucose, liver function test and complete blood count), dietary and exercise advice and adverse drug reactions (ADRs) were recorded by the physician in the case report form.

### Outcome measures

The primary outcome measure was to identify the profile of subjects who were recommended NS-YGP. The secondary outcome measures were to evaluate the changes in laboratory parameters and BMI from baseline to 3 and 6 months and determine ADRs, if any. The data were also stratified based on age (18-30 years, 41-50 years, 51-60 years and ≥61 years) and gender (males and females) groups.

### Statistical analyses

A total of 2000 subjects were planned to be included in the study, considering a drop-out rate of more than 50% due to the nature of study design and a long follow-up period. The descriptive statistics were used to analyze the study results. The continuous variables were presented as mean ± standard deviation and the categorical variables as frequencies and percentages.

The changes in lipid parameters from baseline to 3 and 6 months were evaluated by paired t-test. The other laboratory parameters were compared at different time points by using repeated measures of analysis of variance (ANOVA) with time as a factor. The proportion of subjects having different comorbidities were compared between males and females and different age groups using Chi-square test. The changes in the levels of lipid and other laboratory parameters, BMI, body weight and vitals over 6 months between males and females and different age groups were assessed by one-way ANOVA with sub-groups as the factor. A P-value of $< 0.05$ was considered statistically significant. All the statistical analyses were performed using SAS version 9.4.

## Results

### Baseline Data

A total of 573 subjects, against a planned sample size of 2000 subjects, were enrolled into the study due to low recruitment rate. Out of 573 subjects, 527 (92%) subjects completed the study and were included in the statistical analysis.

The mean age of the subjects was 50 ± 11.5 years. More than 20% of the subjects had an age in the range of 41-50 years (28.8%), 51-60 years (28.4%) and ≥ 61 years (20.8%). Majority of the subjects were males (76.6%), married (97.7%), qualified as graduate/post-graduate (55.5%) and non-obese (85.9%). The details on other baseline features are presented in Table 1.

Five hundred and forty-three (94.8%) subjects had 1 or more comorbidities at the time of entry into the study, of which, 87.3% had borderline dyslipidemia followed by diabetes mellitus (25.8%) and hypertension (19.7%). There was a statistically significant difference in the frequency of comorbid conditions between males and females ($p = 0.0195$) and different age groups ($p < 0.0001$) (Table 2).

Prior to enrolment into the study, 503 (87.8%) subjects were already on

**Table 1: Baseline characteristics**

| Parameters | ITT population (N=573) |
|---|---|
| Age (years), mean ± SD (range) | 50 ± 11.5 (23.0, 86.0) |
| Age Groups, n (%) | |
| 18 – 30 years | 26 (4.5) |
| 31 – 40 years | 100 (17.5) |
| 41 – 50 years | 165 (28.8) |
| 51 – 60 years | 163 (28.4) |
| 61 years and above | 119 (20.8) |
| Missing | 1 (0.2) |
| Gender, n (%) | |
| Male: Females | 439 (76.6): 134 (23.4) |
| Height (cm), mean ± SD (range) | 164 ± 7.7 (140.0, 183.0) |
| Weight (kg), mean ± SD (range) | 71 ± 11.2 (39.0, 136.0) |
| BMI (kg/m$^2$), mean ± SD (range) | 26 ± 4.0 (15.6, 47.0) |
| BMI Categories, n (%) | |
| Non-Obese: Obese | 492 (85.9): 84 (14.7) |
| Marital status, n (%)[1] | |
| Married: unmarried | 560 (97.7): 13 (2.3) |
| Education, n (%) | |
| Profession or honours | 58 (10.1) |
| Graduate or post-graduate | 318 (55.5) |
| Intermediate or post-high school drop | 65 (11.3) |
| High school certificate | 57 (9.9) |
| Middle school certificate | 47 (8.2) |
| Primary school certificate | 23 (4.0) |
| Illiterate | 5 (0.9) |
| Occupation, n (%) | |
| Professional | 182 (31.8) |
| Semi-professional | 91 (15.9) |
| Clerical, shop-owner | 107 (18.7) |
| Skilled worker | 22 (3.8) |
| Semi-skilled worker | 30 (5.2) |
| Unskilled worker | 17 (3.0) |
| Unemployed | 124 (21.6) |
| Monthly family income (INR), n (%) | |
| ≥ 36017 | 188 (32.8) |
| 18000-36016 | 182 (31.8) |
| 13495-17999 | 78 (13.6) |
| 8989-13494 | 54 (9.4) |
| 5387-8988 | 43 (7.5) |
| 1803-5386 | 9 (1.6) |
| ≤ 1802 | 18 (3.1) |
| Missing | 1 (0.2) |
| Personal habits, n (%) | |
| Alcohol | 31 (5.4) |
| Smoking | 31 (5.4) |
| Tobacco chewing | 33 (5.8) |
| Missing | 478 (83.4) |
| Diet and exercise advised to subjects, n (%) | 424 (74) |
| Vital sign, mean ± SD (range) | |
| Pulse rate (/min) | 85.2 ± 9.65 (55, 120) |
| Respiratory rate (/min) | 17.4 ± 3.49 (12, 32) |
| Systolic blood pressure (mmHg) | 131.9 ± 12.80 (100, 200) |
| Diastolic blood pressure (mmHg) | 79.9 ± 8.72 (60, 120) |
| Comorbid conditions, n (%) | 543 (94.8) |
| Dyslipidaemia | 500 (87.3) |
| Diabetes mellitus | 148 (25.8) |
| Obesity | 8 (1.4) |
| Asthma | 0 |
| Autoimmune disorder | 1 (0.2) |
| Stroke | 1 (0.2) |
| Hypertension | 113 (19.7) |
| Skin disorders | 0 |
| CHD / IHD | 18 (3.1) |
| Nephropathy / CKD | 1 (0.2) |
| Cancer | 0 |
| Others | 20 (3.5) |
| Arthritis | 1 (0.2) |
| COPD | 1 (0.2) |
| Dietary supplement | 1 (0.2) |
| Hypertension | 8 (1.4) |
| Hypothyroid | 6 (1.1) |
| Hypothyroidism | 1 (0.2) |
| PTCA | 1 (0.2) |
| Tuberculosis | 1 (0.2) |
| Vitamin D deficiency | 0 |

[1]Non-obese subjects had BMI ≤ 30 and obese had BMI ≥ 30. Three subjects had BMI as 30 kg/m$^2$. Hence, these 3 subjects had been included in both obese and non-obese categories. PTCA: Percutaneous transluminal coronary angioplasty

NS-YGP. During study peroid, >5% of subjects received Metformin (17.5%), Glimepiride (9.8%), Atorvastatin (8.4%), Telmisartan (6.1%) and Rosuvastatin (6.0%) for management of their comorbid conditions.

### *Effect of* NS-YGP *on different parameters*

#### *Lipid Profile*

Treatment with NS-YGP resulted in a significant reduction in total cholesterol (TC) from 215.5 ± 47.0 mg/dL at baseline to 190.4 ± 35.8 mg/dL at month 3 (p < 0.0001) and 178.2 ± 30.0 mg/dL at month 6 (p < 0.0001). The similar results were observed when the data of LDL-C, non-HDL-C and triglycerides (TG) were evaluated from baseline to 3 and 6 months (LDL-C: 130.5 ± 33.9 mg/dL [at baseline] to 110.9 ± 27.8 mg/dL and 103.7 ± 25.0 mg/dL at months 3 and 6, respectively [p < 0.0001]; non-HDL-C: 127.6 ± 65.6 mg/dL [at baseline] to 107.8 ± 53.2 mg/dL and 94.4 ± 46.1 mg/dL at months 3 and 6, respectively [p < 0.0001]; TG: 199.5 ± 83.7 mg/dL [at baseline] to 164.1 ± 51.6 mg/dL and 152.8 ± 40.1 mg/dL at months 3 and 6, respectively [p < 0.0001]). In addition, there was an increase, though non-significant, in HDL-C level from 45.0 ± 14.5 at baseline to 45.9 ± 11.1 mg/dL at month 3 (p = 0.17) and a significant increase to 47.5 ± 9.9 mg/dL at month 6 (p = 0.0007) (Table 3 and Figure 2).

The changes in mean levels of lipid parameters from baseline to months 3 and 6 were compared between males and females (Table 4) and different age groups (Table 5). There was a statistically significant difference in the levels of TC and LDL-C from baseline to month 3 (TC: p=0.01; LDL-C: p=0.004) and in LDL-C level from baseline to month 6 (p=0.04) between males and females (Table 4).

The data by age groups revealed a statistically significant difference in the levels of LDL-C and HDL-C from baseline to month 3 between different age groups (LDL-C: p=0.003; HDL-C: p=0.009). In addition, the change in HDL-C from baseline to month 6 was also significantly different between age groups (p=0.004) (Table 5).

#### *Other Laboratory Parameters*

NS-YGP resulted in statistically significant differences in the levels of creatine phosphokinase (CPK), serum creatinine, hemoglobin (Hb) and white blood cells (WBC) from baseline to 3 and 6 months (p<0.05). In addition, statistically significant differences in red blood cells (RBC) and platelet counts were also observed from baseline to month 6 (Table 6).

There were no statistically significant differences observed in blood glucose levels (fasting glucose, postprandial glucose, random glucose and glycated hemoglobin), liver function tests (CPK, alanine aminotransferase, aspartate aminotransferase, total bilirubin) and complete blood counts (Hb, WBC, RBC, platelet count, creatine kinase) from baseline to 3 and 6 months between males and females and different age groups. However, a statistically significant differences in serum creatinine from baseline to month 6 and Hb level and RBC counts from baseline to 3 and 6 months were recorded between males and females (data not shown).

#### *Body weight and BMI*

There were no statistically significant changes in the body weight and BMI from baseline to 3 and 6 months among

gender and different age groups (data not shown).

*Vital signs*

There were statistically significant differences in pulse rate (p = 0.004) and systolic blood pressure (p = 0.001) from baseline to month 3 between males and females. However, other vital signs were not statistically different from baseline to 3 and 6 months between subjects of different age groups (data not shown).

*Dietary and exercise advice*

The dietary and exercise advice to the subjects increased from baseline (74%) to month 3 (75.1%) and month 6 (83.8%).

*Adverse drug reactions*

NS-YGP was well-tolerated over 6 months of the study treatment. No adverse drug reactions were reported in the study.

## Discussion

In recent years, lack of balanced diet and physical activities, unhealthy lifestyle and spiking stress are ominously increasing the risk of CVD, even among youngsters.[10] Patients with CV risk adopt alternative therapies probably due to an intolerance to the standard therapies, unwillingness to long duration treatments and related psychological barriers.[11] Nowadays, nutraceuticals are gaining popularity and may be considered an alternative treatment in view of its better tolerance and safety profile.[12] NS-YGP is one such nutraceutical which is available as a natural way to lower cholesterol in various countries, but the data on profile of subjects who are prescribed with NS-YGP is limited. The present study was sought to assess the subjects' profile who were on NS-YGP along with their benefits on the levels of lipid parameters in the Indian clinical setting.

In the study, majority of the subjects who were prescribed NS-YGP by their physicians or had been taking on their own before enrolment had borderline elevated lipid levels (87.3%). The reason for high prescription of NS-YGP in subjects with borderline elevated lipid levels probably explains its lipid-lowering efficacy and this has been demonstrated in previous literature as well.[13-15] Our study also showed a significant difference in associated comorbidities between males and females and different age groups. This disparity between gender could be attributed to poor compliance and higher negligence rates leading to increased comorbidities in females than males, in spite of the lower number of females in the study (23.4% versus

**Table 2: Comorbid conditions by gender and age groups**

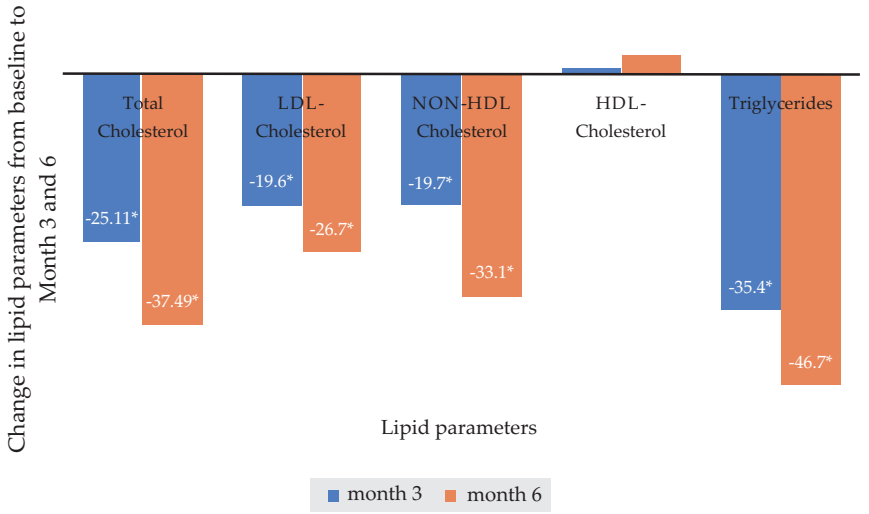
| Comorbid conditions | Gender, n (%) | | Age groups, n (%) | | | | | Total (N=573) n (%) |
|---|---|---|---|---|---|---|---|---|
| | Male (n=439) | Female (n=134) | 18-30 years (n=26) | 31-40 years (n=100) | 41-50 years (n=165) | 51-60 years (n=163) | ≥ 60 years (n=119) | |
| Dyslipidemia | 388 (88.5) | 112 (83.6) | 20 (76.9) | 88 (88.0) | 155 (93.9) | 149 (91.4) | 88 (74.0) | 500 (87.26) |
| Diabetes mellitus | 110 (25.1) | 38 (28.4) | 8 (30.77) | 16 (16.0) | 46 (27.9) | 46 (28.2) | 32 (26.9) | 148 (25.83) |
| Hypertension | 77 (17.5) | 36 (26.9) | 7 (26.9) | 11 (11.0) | 31 (18.8) | 36 (22.1) | 28 (23.5) | 113 (19.72) |
| Obesity | 4 (0.9) | 4 (3.0) | 2 (7.7) | 4 (4.0) | 1 (0.6) | 0 | 1 (0.8) | 8 (1.40) |
| CHD / IHD | 15 (3.4) | 3 (2.2) | 0 | 0 | 4 (2.4) | 5 (3.1) | 9 (7.6) | 18 (3.14) |
| Autoimmune disorder | 1 (0.2) | 0 | 1 (3.85) | 0 | 0 | 0 | 0 | 1 (0.17) |
| Stroke | 0 | 1 (0.8) | 0 | 1 (1.00) | 0 | 0 | 0 | 1 (0.17) |
| Nephropathy / CKD | 1 (0.2) | 0 | 0 | 0 | 0 | 0 | 1 (0.8) | 1 (0.17) |
| Asthma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Skin disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cancer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Others | 10 (2.3) | 10 (7.5) | 1 (3.9) | 6 (6.00) | 4 (2.4) | 6 (3.7) | 3 (2.5) | 20 (3.49) |
| p-value[1] | 0.0195 | | | | < 0.0001 | | | |

[1]p-value was computed using Chi-square test to check the difference of presence of comorbid condition between males and females and different age-groups; CHD/IHD: Coronary heart disease / ischemic heart disease; CKD: chronic kidney disease

**Table 3: Change in the levels of lipid parameters from baseline to Months 3 and 6**

| | Baseline (N=573) | Month 3 (N=525) | Change from baseline | Month 6 (N=451)[1] | Change from baseline |
|---|---|---|---|---|---|
| Total cholesterol, mg/dL | | | | | |
| N | 294 | 294 | 294 | 294 | 294 |
| Mean (SD) (range) | 215.5 (47.0) (77.00, 361.00) | 190.4 (35.8) (99.00, 300.00) | -25.11 (28.63) (-159.00, 83.00) | 178.2 (30.0) (85.00, 289.00 | -37.49 (42.2) (-175.00, 128.00) |
| p-value[2] | | | <0.0001* | | <0.0001* |
| Low-density lipoprotein-cholesterol, mg/dL | | | | | |
| N | 295 | 295 | 295 | 295 | 295 |
| Mean (SD) (range) | 130.5 (33.9) (23.60, 230.00) | 110.9 (27.8) (10.00, 185.30) | -19.6 (24.0) (-120.00, 82.00) | 103.7 (25.0) (22.60, 183.50) | -26.7 (32.6) (-109.00, 116.60) |
| p-value[2] | | | <0.0001* | | <0.0001* |
| Non-high-density lipoprotein-cholesterol, mg/dL | | | | | |
| N | 213 | 213 | 213 | 213 | 213 |
| Mean (SD) (range) | 127.6 (65.6) (14.00, 274.00) | 107.8 (53.2) (16.00, 242.00) | -19.7 (25.1) (-113.00, 76.00) | 94.4 (46.1) (16.00, 203.00) | -33.1 (34.5) (-170.00, 55.00) |
| p-value[2] | | | <0.0001* | | <0.0001* |
| High-density lipoprotein-cholesterol, mg/dL | | | | | |
| N | 287 | 287 | 287 | 287 | 287 |
| Mean (SD) (range) | 45.0 (14.5) (19.00, 102.70) | 45.9 (11.1) (28.00, 96.90) | 0.9 (10.7) (-35.00, 53.00) | 47.5 (9.9) (26.00, 89.40) | 2.5 (12.2) (-33.00, 40.00) |
| p-value[2] | | | 0.17 | | 0.0007* |
| Triglycerides, mg/dL | | | | | |
| N | 292 | 292 | 292 | 292 | 292 |
| Mean (SD) (range) | 199.5 (83.7) (41.90, 763.00) | 164.1 (51.6) (40.50, 389.00) | -35.4 (64.7) (-638.00, 171.00) | 152.8 (40.1) (55.80, 267.00) | -46.7 (68.5) (-573.00, 47.00) |
| p-value[2] | | | <0.0001* | | <0.0001* |

[1]Lipid profile data was not available for 76 subjects at month 6. Hence, lipid profile of 451 subjects was evaluated at month 6. [2]p-value was calculated by paired t-test (*statistically significant).




*Statistically significant (p<0.0001)

**Fig. 2: Change in lipid parameters from baseline to visits 2 and 3**

76.6%).[16] NS-YGP was used in a higher proportion of subjects aged 41-60 years (both inclusive) than the subjects of other age categories. It is evident that subjects under this age category are reluctant to chronic drug intake due to its side-effects and more inclined towards herbal or other alternative regimes of natural origin.[17]

### Lipid-lowering efficacy, safety and mechanism

NS-YGP treatment is associated with statistically significant decline in the levels of triglyceride, TC, LDL-C, and non-HDL-C over 3 and 6 months. The maximum reduction was noted in the mean levels of triglycerides (35.4 mg/dL) followed by TC (25.1 mg/dL), non-HDL-C (19.7 mg/dL) and LDL-C (19.6 mg/dL) following 3 months treatment. Triglycerides was reduced by 46.7 mg/dL followed by TC (37.4 mg/dL), non-HDL-C (33.1 mg/dL) and LDL-C (26.7 mg/dL) at 6 months follow-up. The present findings are consistent with the previous studies where red yeast rice (RYR), a key ingredient of NS-YGP, demonstrated a substantial lipid-lowering efficacy in dyslipidemia patients.[13-15] In ESSENS dyslipidemia study, nearly 30% reduction was reported in LDL-C and non-HDL-C levels following 3-month NS-YGP therapy in subjects with newly diagnosed hyperlipidemia.[13] Furthermore, a significant reduction in TC ($p < 0.0001$) and triglycerides ($p = 0.01$) were also observed from baseline to week 12.[13] In another trial, RYR resulted in a significant decrease in LDL-C from baseline (163.3 mg/dL) to week 12 (120 mg/dL) and week 24 (128.3 mg/dL) in patients who discontinued statin therapy because of associated myalgia.[14] Similarly, Verhoeven et al (2013) reported 22% reduction in LDL-C and 15% reduction in TC with RYR, as compared with placebo over a period of 8 weeks.[15] However, it should be noted that the lifestyle change program, such as diet and exercise advised to subjects must have imposed an additive effect to reach favorable serum lipid levels in the studied population.

Age and gender have shown a profound effect on lipid profiles; hence we evaluated these factors between different age and gender groups. Females had shown significantly higher reduction in mean LDL-C at both month 3 ($P = 0.004$) and month 6 ($P = 0.04$), compared to males. However, TC was significantly reduced in females at month 3 ($P = 0.01$) only. The finding suggests that NS-YGP reduces LDL-C and TC more effectively in females than males. This might be due to the fact that females once on treatment, diligently and strictly follows physician advise and takes proper dosage of treatment while males are more reluctant to embark on dietary and lifestyle changes.[18] When analyzing subjects according to the age groups, maximum reduction in LDL-C was observed in the age-group of 18-30 years (28.96 mg/dL) and a maximum increase in HDL-C was noted in the age group of 31-40 years (4.49 mg/dL) over 3 months. The higher acceptability of NS-YGP among middle-aged subjects is probably due to herbal nature of the drug.

NS-YGP consists of different bioactive ingredients derived from food and have distinct pharmacologic activities. The substantial lipid-lowering effects with this nutraceutical are the result of synergistic action of all the ingredients (niacin, folic acid, grape seed, black pepper seed powder and red yeast rice). Red yeast rice contains a milieu of monacolins, including naturally occurring lovastatin (monacolin K), which inhibits 3-hydroxy-3-methyl glutaryl coenzyme A reductase and contributes to lipid-lowering effects.[13,14] In our study no safety concerns were observed with NS-YGP over 6 months of follow-up.

### Clinical implication of the findings

It is noteworthy that the reduction in levels of triglycerides over a period of 3-month following NS-YGP treatment is substantially higher in our study (35.4 mg/dL) than ESSENS dyslipidemia study (24 mg/dL). This indicates that NS-YGP might hold a promise for people with high triglycerides level. This is especially important in Indian patients, given that they consume too much of carbohydrate which resulting in high level of triglycerides.[19] However, this needs to be ascertained by investigation in controlled trials. Moreover, unlike statins where myopathy occurs in approximately 10% of patients, NS-YGP does not produce any episode of myalgia in any of the patients during the study period.[20] This is possibly due to low dose of monacolin K (lovastatin) in NS-YGP which is below the threshold necessary to cause statin-associated myalgia.[13] Also, a combination of nutraceuticals with different but synergistic mechanisms, at lower and safer dosages, are preferred over the full dose of nutraceuticals which can entail some tolerability concerns. This finding has clinical relevance in patients who have statin intolerance and withdraws due to myopathy. NS-YGP may be used as an alternative therapy in patients with a history of statin-related adverse effects or when statins alone are not able to bring about desired LDL-C reduction as there is a scarcity of effective pharmacologic options that could be used in place of or in combination with statin therapy.[21]

**Table 4: Change from baseline to months 3 and 6 for lipid parameters among genders**

| Parameters | | Baseline (N=573) | Month 3 (N=525) | Change from baseline | Month 6 (N=451)[1] | Change from baseline |
|---|---|---|---|---|---|---|
| Total cholesterol | | | | | | |
| Male | n, Mean ± SD (range) | 420, 186.60 ± 46.64 (77.00, 361.00) | 323, 176.15 ± 35.91 (99.00, 300.00) | 313, -17.86 ± 30.39 (-159.00, 83.00) | 222, 176.86 ± 30.20 (85.00, 265.00) | 209, -34.35 ± 44.84 (-175.00, 128.00) |
| | Missing | 19 | 116 | 126 | 217 | 230 |
| Female | n, Mean ± SD (range) | 126, 207.69 ± 44.68 (110.00, 331.00) | 112, 186.30 ± 32.87 (116.50, 289.00) | 111, -25.78 ± 23.87 (-96.00, 35.00) | 99, 177.80 ± 30.85 (102.00, 289.00) | 95, -41.69 ± 36.66 (-143.00, 61.00) |
| | Missing | 8 | 22 | 23 | 35 | 39 |
| p-value[2] | | | | 0.01* | | 0.16 |
| LDL-Cholesterol | | | | | | |
| Male | n, Mean ± SD (range) | 421, 119.48 ± 28.05 (23.60, 230.00) | 322, 109.14 ±24.59 (10.00, 185.30) | 313, -13.01 ± 23.95 (-120.00, 82.00) | 221, 103.89 ± 25.54 (22.60, 170.20) | 208, -23.72 ± 34.36 (-109.00, 116.60) |
| | Missing | 18 | 117 | 126 | 218 | 231 |
| Female | n, Mean ± SD (range) | 126, 129.86 ± 31.38 (71.00, 221.00) | 113, 110.78 ±22.71 (62.00, 184.00) | 112, -20.50 ±21.99 (-86.00, 28.00) | 99, 102.45 ±23.94 (51.00, 183.50) | 95, -31.92 ± 28.98 (-104.00, 54.70) |
| | Missing | 8 | 21 | 22 | 35 | 39 |
| p-value[2] | | | | 0.004* | | 0.04* |
| Non-HDL-Cholesterol | | | | | | |
| Male | n, Mean ± SD (range) | 354, 126.08 ± 49.05 (14.00, 274.00) | 264, 114.79±44.22 (16.00, 242.00) | 259, -12.02 ± 29.61 (-113.00, 131.30) | 161, 94.22 ±46.46 (16.00, 203.00) | 154, -31.72 ± 36.16 (-170.00, 55.00) |
| | Missing | 85 | 175 | 180 | 278 | 285 |
| Female | n, Mean ± SD (range) | 89, 131.38± 56.35 (20.00, 249.00) | 81, 107.76±46.91 (16.00, 190.00) | 76, -18.12 ± 29.01 (-93.36, 94.00) | 66, 93.27 ± 44.36 (19.00, 163.00) | 63, -35.38± 31.35 (-102.08, 34.00) |
| | Missing | 45 | 53 | 58 | 68 | 71 |
| p-value[2] | | | | 0.11 | | 0.48 |
| HDL-Cholesterol (HDL-C) | | | | | | |
| Male | n, Mean ± SD (range) | 419, 50.59±14.17 (19.00, 102.70) | 322, 51.18±12.70 (28.00, 96.90) | 309, 1.65 ± 11.00 (-35.00, 53.00) | 217, 47.67 ± 9.67 (26.00, 89.40) | 203, 2.48 ±12.12 (-33.00, 38.10) |
| | Missing | 20 | 117 | 130 | 222 | 236 |
| Female | n, Mean ± SD (range) | 123, 48.18 ±14.69 (23.00, 90.00) | 109, 47.14 ±12.80 (22.00, 86.00) | 106, 0.10 ± 10.90 (-27.00, 46.00) | 97, 47.83 ±10.44 (30.00, 82.50) | 93, 2.74 ±12.26 (-29.00, 40.00) |
| | Missing | 11 | 25 | 28 | 37 | 41 |
| p-value[2] | | | | 0.21 | | 0.87 |
| Triglycerides (TG) | | | | | | |
| Male | n, Mean ± SD (range) | 414, 176.13 ± 72.80 (41.90, 763.00) | 322, 161.02 ±47.48 (40.50, 418.10) | 309, -23.41 ±64.40 (-638.00, 183.10) | 219, 155.17 ±39.22 (68.00, 267.00) | 204, -49.97± 75.98 (-573.00, 120.00) |
| | Missing | 25 | 117 | 130 | 220 | 235 |
| Female | n, Mean ± SD (range) | 124, 175.78 ± 65.02 (58.00, 459.00) | 113, 154.10 ±44.49 (41.90, 280.00) | 111, -26.22 ±45.57 (-350.00, 39.00) | 98, 147.55 ±39.84 (55.80, 200.40) | 95, -38.36 ±51.90 (-261.00, 45.40) |
| | Missing | 10 | 21 | 23 | 36 | 39 |
| p-value[2] | | | | 0.67 | | 0.18 |

HDL: High-density lipoprotein; LDL: Low-density lipoprotein. [1]Lipid profile data was not available for 76 subjects at visit 3. Hence, lipid profile of 451 subjects was evaluated at month 6. [2]p-value was calculated using one-way ANOVA with gender as the factor on change from baseline at visit 2 and visit 3.
*statistically significant.

## Strengths and Limitations

The study has few strengths and limitations. The strengths being that ours is the first PAN-India study assessing the profile of subjects prescribed with NS-YGP in the Indian clinical setting. Also, the patients were recruited during a regular visit to their general practitioner ensuring homogeneity of the sociodemographic variables. Additional analysis was performed to summarize the efficacy of NS-YGP in males and females and different age-groups subjects. However, there were few limitations of the study as well. First, it was an open-label observational study, which limited the viability of our results so confounding factors affecting its outcomes cannot be excluded. Secondly, the study was prematurely terminated after enrolment of 573 subjects, against a planned sample size of 2000 subjects. Lastly, the study could not assess the incremental reduction in lipid parameters in patients already on statin therapy.

## Conclusion

Most of the subjects prescribed with NS-YGP had borderline elevated lipid levels. It was found most effective in lowering triglycerides, followed by LDL-C, Non-HDL-C, and TC after 3-and 6-month treatment. Also, it significantly increased HDL-C levels following 6-month treatment. This allows to consider that NS-YGP regulates triglycerides levels in borderline cases and can prevent or delay them to convert on dyslipidemia. It has a clinical relevance in Indian patients, given that they have more intake of carbohydrate rich food which raises their triglycerides level. NS-YGP formulation was also well-tolerated and can be recommended in the primordial prevention of borderline dyslipidemia. Further investigation for in-depth understanding of long-term safety, use in special population, including children, the elderly and pregnant women, and its pharmacological interaction with other drugs need to be more closely assessed.

## Funding

The study was funded by Abbott Healthcare India Pvt. Limited.

**Table 5: Change from baseline to months 3 and 6 for lipid parameters among different age groups**

| Age groups (years) | | Baseline (N=573) | Month 3 (N=525) | Change from Baseline | Month 6 (N=451)[1] | Change from Baseline |
|---|---|---|---|---|---|---|
| Total cholesterol | | | | | | |
| 18-30 | n, Mean ± SD (range) | 25, 232.46 ± 48.86 (115.00, 306.80) | 25, 201.20 ± 42.03 (103.00, 281.00) | 25, -31.26 ± 34.54 (-107.00, 47.00) | 23, 188.67 ± 41.30 (110.00, 289.00) | 22, -43.18 ± 44.87 (-96.30, 83.00) |
| | Missing | 1 | 1 | 1 | 3 | 4 |
| 31-40 | n, Mean ± SD (range) | 100, 193.47 ± 44.80 (94.00, 319.00) | 83, 178.18 ± 31.68 (99.00, 285.00) | 83, -20.30 ± 31.31 (-159.00, 36.00) | 61, 178.36 ± 28.39 (85.00, 250.00) | 61, -31.15 ± 45.17 (-175.00, 65.00) |
| | Missing | 0 | 17 | 17 | 39 | 39 |
| 41-50 | n, Mean ± SD (range) | 163, 193.88 ± 48.64 (87.00, 361.00) | 127, 183.49 ± 35.47 (111.00, 300.00) | 127, -20.00 ± 28.10 (-104.80, 83.00) | 96, 180.30 ± 30.89 (102.00, 265.00) | 95, -38.88 ± 40.61 (-143.00, 128.00) |
| | Missing | 2 | 38 | 38 | 69 | 70 |
| 51-60 | n, Mean ± SD (range) | 154, 187.82 ± 43.94 (124.00, 346.00) | 117, 173.95 ± 35.65 (110.00, 284.00) | 112, -20.11 ± 27.87 (-113.00, 57.00) | 88, 172.72 ± 28.65 (100.00, 250.00) | 82, -36.05 ± 39.91 (-157.00, 61.00) |
| | Missing | 9 | 46 | 51 | 75 | 81 |
| ≥61 | n, Mean ± SD (range) | 104, 181.31 ± 45.52 (77.00, 301.00) | 83, 172.14 ± 33.38 (105.00, 278.00) | 77, -15.52 ± 27.26 (-93.00, 46.00) | 53, 172.42 ± 27.72 (116.00, 264.00) | 44, -37.27 ± 47.28 (-129.00, 76.00) |
| | Missing | 15 | 36 | 42 | 66 | 75 |
| p-value[2] | | | | 0.23 | | 0.77 |
| Low-density lipoprotein-cholesterol | | | | | | |
| 18-30 | n, Mean ± SD (range) | 25, 138.20 ± 43.96 (46.70, 230.00) | 25, 109.24 ± 34.59 (50.10, 184.00) | 25, -28.96 ± 29.64 (-88.00, 33.40) | 23, 101.89 ± 31.61 (45.00, 165.00) | 22, -35.12 ± 31.18 (-96.00, 14.60) |
| | Missing | 1 | 1 | 1 | 3 | 4 |
| 31-40 | n, Mean ± SD (range) | 100, 119.85 ± 29.58 (23.60, 221.00) | 83, 108.29 ± 22.23 (30.00, 172.90) | 83, -13.00 ± 23.68 (-75.20, 61.00) | 61, 104.27 ± 24.10 (32.00, 183.50) | 61, -19.75 ± 33.70 (-98.10, 74.00) |
| | Missing | 0 | 17 | 17 | 39 | 39 |
| 41-50 | n, Mean ± SD (range) | 163, 122.67 ± 26.05 (37.00, 209.00) | 127, 110.08 ± 21.66 (19.00, 162.50) | 127, -14.79 ± 21.39 (-86.00, 82.00) | 96, 101.93 ± 22.11 (45.00, 153.60) | 95, -28.36 ± 33.31 (-109.00, 116.60) |
| | Missing | 2 | 38 | 38 | 69 | 70 |
| 51-60 | n, Mean ± SD (range) | 154, 124.32 ± 28.32 (60.00, 214.00) | 117, 109.46 ± 27.53 (10.00, 185.30) | 113, -17.64 ± 24.78 (-120.00, 55.00) | 88, 104.05 ± 27.02 (22.60, 170.20) | 82, -29.78 ± 32.38 (-103.40, 52.60) |
| | Missing | 9 | 46 | 50 | 75 | 81 |
| ≥61 | n, Mean ± SD (range) | 105, 115.06 ± 28.65 (26.00, 195.00) | 83, 110.28 ± 20.84 (46.00, 184.70) | 77, -9.02 ± 21.45 (-84.00, 43.00) | 52, 104.94 ± 25.25 (52.00, 168.10) | 43, -19.81 ± 31.76 (-80.00, 62.40) |
| | Missing | 14 | 36 | 42 | 67 | 76 |
| p-value[2] | | | | 0.003* | | 0.14 |
| Non-high-density lipoprotein-cholesterol | | | | | | |
| 18-30 | n, Mean ± SD (range) | 13, 162.85 ± 58.97 (18.00, 242.00) | 14, 137.67 ± 49.00 (20.00, 215.00) | 13, -26.16 ± 21.77 (-62.00, 6.00) | 13, 114.13 ± 44.89 (16.40, 203.00) | 13, -48.71 ± 25.67 (-95.00, -1.60) |
| | Missing | 13 | 12 | 13 | 13 | 13 |
| 31-40 | n, Mean ± SD (range) | 85, 125.48 ± 54.15 (17.00, 253.00) | 68, 110.28 ± 47.43 (20.00, 200.00) | 68, -12.96 ± 32.23 (-113.00, 90.00) | 50, 88.09 ± 48.07 (16.00, 163.00) | 49, -34.67 ± 37.42 (-170.00, 25.90) |
| | Missing | 15 | 32 | 32 | 50 | 51 |
| 41-50 | n, Mean ± SD (range) | 132, 123.47 ± 47.75 (19.00, 254.00) | 102, 109.22 ± 43.87 (16.00, 190.00) | 100, -10.88 ± 27.01 (-87.00, 94.00) | 68, 87.47 ± 42.61 (19.60, 160.00) | 65, -29.03 ± 27.46 (-99.00, 34.00) |
| | Missing | 33 | 63 | 65 | 97 | 100 |
| 51-60 | n, Mean ± SD (range) | 127, 126.20 ± 51.96 (20.00, 274.00) | 98, 114.73 ± 46.50 (16.00, 242.00) | 93, -13.05 ± 28.84 (-93.36, 77.00) | 66, 98.56 ± 45.36 (19.00, 159.00) | 62, -29.64 ± 40.84 (-140.00, 55.00) |
| | Missing | 36 | 65 | 70 | 97 | 101 |
| ≥61 | n, Mean ± SD (range) | 86, 130.44 ± 46.56 (14.00, 254.00) | 63, 114.63 ± 39.45 (19.00, 208.00) | 61, -15.87 ± 32.73 (-80.00, 131.30) | 30, 99.46 ± 48.54 (16.00, 167.00) | 28, -37.74 ± 33.76 (-103.52, 25.00) |
| | Missing | 33 | 56 | 58 | 89 | 91 |
| p-value[2] | | | | 0.46 | | 0.32 |
| High-density lipoproteins-cholesterol | | | | | | |
| 18-30 | n, Mean ± SD (range) | 25, 51.75 ± 17.15 (22.00, 90.00) | 25, 48.15 ± 10.72 (35.00, 74.00) | 25, -3.61 ± 11.27 (-18.00, 29.00) | 23, 49.73 ± 10.93 (26.00, 82.50) | 22, -3.00 ± 14.09 (-28.00, 28.00) |
| | Missing | 1 | 1 | 1 | 3 | 4 |
| 31-40 | n, Mean ± SD (range) | 99, 46.92 ± 14.16 (19.00, 90.00) | 82, 49.69 ± 14.31 (29.00, 86.00) | 81, 4.49 ± 11.35 (-20.00, 46.00) | 58, 48.99 ± 11.25 (30.00, 89.40) | 58, 7.33 ± 12.31 (-15.00, 40.00) |
| | Missing | 1 | 18 | 19 | 42 | 42 |
| 41-50 | n, Mean ± SD (range) | 162, 51.09 ± 13.80 (23.00, 98.00) | 126, 49.93 ± 12.15 (22.00, 79.00) | 125, 0.15 ± 9.87 (-27.00, 31.00) | 94, 46.90 ± 8.86 (30.00, 78.15) | 92, 1.11 ± 11.25 (-33.00, 30.00) |
| | Missing | 3 | 39 | 40 | 71 | 73 |
| 51-60 | n, Mean ± SD (range) | 153, 50.41 ± 14.78 (25.00, 102.70) | 116, 50.04 ± 13.06 (28.00, 96.90) | 111, 1.11 ± 11.15 (-35.00, 53.00) | 88, 47.24 ± 9.29 (31.00, 88.72) | 82, 2.82 ± 12.34 (-29.00, 33.86) |
| | Missing | 10 | 47 | 52 | 75 | 81 |

*Contd..*

**Table 5: Change from baseline to months 3 and 6 for lipid parameters among different age groups *(Contd...)***

| Age groups (years) | | Baseline (N=573) | Month 3 (N=525) | Change from Baseline | Month 6 (N=451)[1] | Change from Baseline |
|---|---|---|---|---|---|---|
| ≥61 | n, Mean ± SD (range) | 103, 50.46 ± 13.64 (22.00, 79.68) | 82, 51.77 ± 12.70 (30.00, 78.00) | 73, 1.45 ± 11.29 (-30.00, 30.00) | 51, 47.72 ± 10.74 (29.00, 72.00) | 42, 1.54 ± 10.58 (-22.00, 26.50) |
| | Missing | 16 | 37 | 46 | 68 | 77 |
| p-value[2] | | | | 0.009* | | 0.003* |
| Triglycerides | | | | | | |
| 18-30 | n, Mean ± SD (range) | 25, 201.06 ± 82.35 (58.00, 439.00) | 25, 179.16 ± 75.65 (41.90, 389.00) | 25, -21.89 ± 54.12 (-129.00, 171.00) | 23, 162.76 ± 50.30 (55.80, 236.00) | 22, -42.18 ± 58.41 (-246.00, 25.00) |
| | Missing | 1 | 1 | 1 | 3 | 4 |
| 31-40 | n, Mean ± SD (range) | 99, 186.15 ± 93.95 (60.00, 763.00) | 83, 159.56 ± 41.57 (82.00, 280.00) | 83, -33.60 ± 96.23 (-638.00, 113.00) | 61, 151.73 ± 40.51 (70.80, 224.70) | 61, -58.43 ± 105.67 (-573.00, 45.40) |
| | Missing | 1 | 17 | 17 | 39 | 39 |
| 41-50 | n, Mean ± SD (range) | 160, 180.21 ± 64.20 (45.00, 427.00) | 127, 163.70 ± 44.66 (41.00, 295.00) | 126, -27.61 ± 44.56 (-302.00, 50.00) | 96, 159.31 ± 38.10 (70.20, 267.00) | 92, -45.01 ± 54.88 (-257.00, 61.00) |
| | Missing | 5 | 38 | 39 | 69 | 73 |
| 51-60 | n, Mean ± SD (range) | 151, 170.46 ± 60.29 (41.90, 376.00) | 118, 153.32 ± 42.63 (40.50, 280.00) | 112, -20.15 ± 37.40 (-134.00, 72.00) | 85, 145.83 ± 35.73 (69.80, 215.00) | 81, -39.81 ± 52.40 (-205.00, 28.00) |
| | Missing | 12 | 45 | 51 | 78 | 82 |
| ≥61 | n, Mean ± SD (range) | 103, 161.98 ± 64.68 (60.00, 459.00) | 82, 154.38 ± 48.15 (77.00, 418.10) | 74, -14.49 ± 59.20 (-350.00, 183.10) | 52, 149.11 ± 40.27 (68.00, 201.00) | 43, -46.06 ± 66.46 (-261.00, 120.00) |
| | Missing | 16 | 37 | 45 | 67 | 76 |
| p-value[2] | | | | 0.29 | | 0.61 |

[1]Lipid profile data was not available for 76 subjects at visit 3. Hence, lipid profile of 451 subjects was evaluated at month 6. [2]p-value was calculated using one-way ANOVA with age group as the factor on change from baseline at visit 2 and visit 3. *statistically significant.

**Table 6: Change in the levels of other laboratory parameters from baseline to months 3 and 6**

| Parameters | Month 3 (least square mean [standard error]) | p-value[1] | Month 6 (least square mean [standard error]) | p-value[1] |
|---|---|---|---|---|
| Blood glucose | | | | |
| Fasting glucose | 0.13 (2.58) | 0.9612 | -3.89 (3.01) | 0.1982 |
| Post prandial glucose | 3.25 (4.35) | 0.4563 | -1.85 (5.15) | 0.7191 |
| Random glucose | 0.25 (3.22) | 0.9389 | -0.49 (3.61) | 0.8918 |
| Acylated haemoglobin | -0.27 (0.29) | 0.3587 | -0.39 (0.12) | 0.0020 |
| Liver function tests | | | | |
| Creatine phosphokinase | 22.37 (5.05) | 0.0001* | 58.89 (4.76) | 0.0001* |
| Alanine aminotransferase | 0.11 (1.11) | 0.9197 | -1.11 (1.19) | 0.3549 |
| Aspartate aminotransferase | -1.00 (0.97) | 0.3061 | -1.21 (1.08) | 0.2648 |
| Serum creatinine | 0.05 (0.015) | 0.0009* | 0.07 (0.017) | <0.0001* |
| Total bilirubin | -0.02 (0.042) | 0.6333 | 0.02 (0.036) | 0.5920 |
| Complete blood count | | | | |
| Hemoglobin | 0.43 (0.11) | 0.0004* | 0.46 (0.13) | 0.0009* |
| White blood cells | -311.2 (134.58) | 0.0211* | -879.1 (152.83) | 0.0001* |
| Red blood cells | 0.07 (0.042) | 0.0995 | 0.12 (0.047) | 0.0093* |
| Platelet count | -2.06 (5.74) | 0.7200 | -19.38 (6.61) | 0.0035* |
| Creatine kinase | 0.99 (0.14) | 0.0001* | Data not available | |

[1]P-value was based on the repeated measures of ANOVA with time as a factor in the model. *statistically significant.

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