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Optimizing Non-Pharmacologic Management of Hypertriglyceridemia

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Abstract

The cornerstone of initial management for hypertriglyceridemia (HTG) is lifestyle modification. The combination of weight loss through caloric restriction, alteration in macronutrient composition and increased energy expenditure reduces TG levels by approximately 50%. The addition of cinnamon, cacao products and isocaloric substitution of 1 serving of nuts may contribute another 5–15% lowering of TG. This can be particularly beneficial in patients with HTG who are at increased risk of cardiovascular disease.

Keywords

Triglycerides; Lifestyle; Weight loss; Diet; Cardiovascular disease

Although westernized societies have witnessed reductions in lipids and lipoproteins in recent years, serum triglyceride (TG) levels remain consistently higher than in developing countries at lower cardiovascular (CVD) risk (1). This is a relevant clinical issue in view of the rising prevalence of obesity, type 2 diabetes mellitus (T2DM2) and insulin resistance coupled with increasing recognition that TG is an important biomarker of CVD risk (2). In fact, a recent meta-analysis of 29 Western prospective studies and 250,000 subjects found an independent association between elevated TG levels and CVD risk (3). An even larger meta-analysis of more than 1 million subjects found that compared to the reference groups with a TG range of 90–149 mg/dL, TG ≥ 150 mg/dL was associated with a 15–25% increased risk of CVD mortality (4). Finally, Mendelian randomization analysis identified common genetic polymorphisms associated with high TG to promote CVD (5). Taken together, high TG has gained a solid foothold as an important biomarker and mediator of CVD risk.

Based upon the aforementioned, the role of TG lowering therapies in potentially offsetting CVD risk is under active investigation. As novel pharmacologic agents continue to be developed and tested, clinicians seek non-pharmacologic alternatives that effectively lower TG. Consequently, this review examines lifestyle measures that provide incremental TG lowering in addition to the recommendations made in the American Heart Association (AHA) scientific statement on TG and CVD (Table 1).

Weight Loss/Dietary Change/Exercise

Weight loss is the most effective non-pharmacologic manner to lower TG levels with a 20% decrease in triglycerides anticipated following 5–10% reduction in body weight (6). It is estimated that for every kilogram of weight loss, one can expect a 2% decrease in TG levels (7). This can serve as a useful education tool for patients with prediabetes or T2DM in whom hypertriglyceridemia (HTG) is common and where an associated 5–10% reduction in body weight may also help to normalize blood glucose levels in a subgroup of patients (8).

While weight loss through caloric restriction and/or increased energy expenditure, represents an important modality for TG reduction, changes in dietary macronutrient composition can also contribute to weight loss and reduction in TG levels. Specifically, a Mediterranean-style diet may result in an approximate 10–15% lowering of TG as compared to a low fat diet. This diet consists of higher consumption of foods rich in monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and dietary fiber through the incorporation of whole grains, vegetables, fruits, nuts and olive oil into the daily diet. In the Framingham Heart Study Offspring Cohort, the highest quintile of the Mediterranean-style dietary pattern was correlated with the lowest TG levels (103 vs. 114 mg/dL, $p < 0.001$) over a seven year follow-up period (9). In fact, adoption of a Mediterranean-style diet has consistently resulted in TG lowering across multiple studies (10–12) this dietary platform has also demonstrated the most robust evidence for CVD prevention (13).

A stalwart of the Mediterranean-style diet is omega-3 (OM3) polyunsaturated fatty acids (PUFAs). Within this class, the marine-derived OM3s, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower TG levels by reducing hepatic output of very low-density lipoprotein (VLDL) (14). PUFAs also induce peroxisome proliferator-activated receptors (PPARs), transcriptional factors involved in the metabolic regulation of lipid and glucose metabolism (15). Dietary sources of these very long-chained PUFAs are illustrated in Table 2 below. Studies suggest that by incorporating approximately 4 g of marine-derived PUFAs to the diet each day, serum TG levels may be reduced 20–30% (16). Overall, there is an approximate 5–10% reduction for each gram of OM3 incorporated into daily food intake (17).

The combination of dietary modification (described above) and aerobic activity accentuates TG lowering via upregulation of lipoprotein lipase (LPL) activity and increased utilization of TG by exercising muscles (2,18). However, the extent of TG lowering is in part, predicated upon baseline TG levels, exercise intensity, caloric expenditure and duration of activity (2). In a study of middle-aged men, participants who ran 7–14 miles per week at a mild to moderate pace (age predicted heart rate ~50–70%) compared to no activity, experienced 20% lower fasting TG levels (mean fasting TG level 106 mg/dL) whereas the highest activity levels (> 20 miles weekly) experienced a 31% decline in TG and lowest mean fasting TG level (86 mg/dL) observed (19). Overall, exercise effectively reduces TG in a dose-response manner, aligned to energy expenditure (2,20). These data support the recommendations that clinicians provide to their patients with HTG—sustained weight loss through lifestyle that includes a Mediterranean-style diet, reduced caloric intake and increased physical activity to yield robust TG reduction and improved metabolic health.

Other Non-Pharmacologic Alternatives

In addition to weight loss, adopting a Mediterranean-style diet and physical activity, other nutrition-based products contribute to TG reduction. They are cinnamon, cocoa/chocolate and certain nuts, most notably hazelnuts.

Cinnamon

Cinnamon increases expression of PPARs alpha and gamma, drug targets for fibrates and thiazolidinediones, respectively (21–23). A meta-analysis in T2DM found that consumption of *Cinnamomum cassia* extract or raw powder (~1 teaspoon daily) up to 18 weeks was associated with an approximate 30 mg/dL decrease in TG and corresponded to reductions in fasting plasma glucose (–25 mg/dL), total cholesterol (–16 mg/dL), LDL-C (–9 mg/dL) and small rise in HDL-C (~2 mg/dL) levels (24). In one of the studies, 6 g of cinnamon (500 mg of ground *Cinnamomum cassia* per capsule) daily for 40 d was associated with a 27% mean TG reduction (219 – > 159 mg/dL) (25). However, with lower doses (3 grams of cinnamon powder) and low baseline TG (173 mg/dL) considerably smaller effects (e.g., 7.5% reduction in TG) have been reported (26).

Cocoa Products

Cocoa products and/or dark chocolate have also been shown in controlled clinical trials to result in an approximate 5% reduction in TG levels (27). It is important to note that these were otherwise healthy individuals (mean age 42 years) without high-TG (mean TG ~ 100 mg/dL) and with treatment duration lasting between 2 and 12 weeks. In a recent meta-analysis comprising 1131 participants, cocoa flavanols showed significant improvement in lipid sensitivity and lipid profile; the amount of flavanols varied from 166–2110 mg/d with intervention period from 2–52 weeks (28). With regard to triglyceride levels, the weighted mean difference between treatment and placebo was 0.10 mmol/L or approximately 9 mg/dL.

Nuts

Nuts consumed in moderation (defined as a serving size of 1 ounce) exert an overall modest effect on TG with a weighted mean reduction of 2.2 mg/dL per serving (29). However, some nuts (e.g., hazelnuts) exhibit more favorable effects. For example, a 2007 study by Mercanligil et al. involving fifteen hypercholesterolemic men aged 48 +/- 8 years showed significant reductions in VLDL cholesterol, TAG and Apo B by ~ 30, 32 and 9%, respectively, while increasing HDL cholesterol concentrations by 12.6% following hazelnut consumption (30). Similar results were shown in a 21 participant study by Orem et al., where 49–86 g of hazelnuts per day over the course of four weeks decreased triglyceride levels by 14% (31).

In addition to hazelnuts, favorable reductions in TG (~30%) have also been observed with pistachios using isocaloric exchange in obese subjects over a three month period (32). Consumption of walnuts, pecans and peanuts has also been shown to be associated with TG reductions in the 10–20% range following isocaloric substitution (33–35). Significant TG

reductions, albeit more modest (5–10%), have been observed with almond consumption (36,37).

Spice Blend

Recent studies have looked into the effects of consuming a high-antioxidant spice blend on post-prandial TG (ppTG) levels; post-prandial being defined as the 4 h time-period following meal consumption. Antioxidant spice blends are thought to ameliorate the deleterious effects of oxidative stress on metabolic parameters (38). An initial pilot study investigated the effect of a single 14 g dose of an antioxidant spice blend on ppTG in 6 overweight, otherwise healthy men (39). The spice blend consisted of black pepper, cinnamon, cloves, garlic powder, ginger, oregano, paprika, rosemary, and turmeric. The results of the study showed a 31% reduction in ppTG after the spiced meal in comparison to the placebo meal. These results were confirmed with a larger study that enrolled 20 overweight or obese, otherwise healthy men and women (40). In addition to replicating previous results, this study demonstrated that *in vitro*, cinnamon, turmeric, and cloves were potent inhibitors of pancreatic lipase and phospholipase A₂, two digestive enzymes involved in lipid absorption in the digestive tract. This particular finding is suggestive of the mechanism by which the spice blend is able to exert a hypolipidemic effect.

Soy

Soy is an additional food source found to play a role in improving serum lipids. Whole soy products consist of protein, phytochemicals, and lipids. Studies have shown a synergistic effect of each of these compounds on serum lipids, whereas individually, each soy component has little effect on improving dyslipidemia (41). The phytochemicals found in soy, such as isoflavones, are thought to bind to estrogen receptors in the body, causing the isoflavone-estrogen receptor complex to translocate to the nucleus where it can then serve as a ligand receptor for proteins involved in lipid regulation, such as PPAR (42,43). Additionally, soy lipids, such as lecithin and phospholipids, produce a hypolipidemic by solubilizing cholesterol in the intestines and consequently, inhibiting cholesterol absorption and promoting excretion (44).

A recent meta-analysis including 2670 participants studied the effects of soy products on serum lipids. Subjects in the experimental groups consumed a daily average of ~30 g of soy products with treatment duration lasting from 4–52 weeks (41). The results of the study showed that there was a statistically significant decrease in serum triglyceride levels (–4.92 mg/dL, 95% CI –8.35, –2.30). Furthermore, the study demonstrated that participants who were hypercholesterolemic at baseline had a more profound decrease in serum LDL-C (–7.47 mg/dL, 95% CI –11.79) than did normolipidemic participants (–2.96 mg/dL, 95% CI –5.28, –0.65). Another study compared the effect of 12 weeks of a low glycemic index diet (LGID) supplemented with 30 g of soy proteins and 4 g phytosterols per day on serum lipids in comparison to the American Heart Association diet in postmenopausal women (45). Participants who completed the LGID with soy product supplementation showed a ~45% decrease in TG, a ~16% decrease in TC, and a ~15% decrease in LDL, further supporting the beneficial effects of whole soy products on serum lipids.

Turmeric

Turmeric is a spice that has been noted for its effect on improving metabolic syndrome parameters. Specifically, the active ingredient curcumin is thought to contribute to the hypolipidemic effect of turmeric. In one study, a ~29% reduction from baseline TG was noted in 33 metabolic syndrome patients consuming 1890 mg daily of curcumin extract for 12 weeks (46). This study found an additional significant effect on serum lipids with a ~10% decrease in TC, ~12% decrease in LDL, and a ~6% increase in HDL ($p < 0.005$ for all). Similarly, the Chuengsamarn et al. study showed a ~47% decrease in TG in 33 Type 2 diabetic patients consuming 1500 mg of curcumin extract daily for a six month period (47).

Conclusions

Overall, lifestyle adjustments play a large and important role in management of hypertriglyceridemia. A 50% reduction in serum triglyceride levels has been shown to occur with weight loss, dietary changes and exercise. The addition cinnamon, cacao products, isocaloric substitution of ~1 ounce of selected nuts, an antioxidant spice blend, soy, and/or turmeric may contribute additional TG lowering. This can be especially important in patients with HTG seeking to optimize lifestyle practices with or without pharmacologic intervention.

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Table 1.

Several Non-Pharmacologic methods for reducing TG levels

Dietary change	TG lowering
Body Weight loss of 5–10%	20%
Mediterranean-style versus high-carbohydrate diet	10–15%
Addition of marine-derived PUFA (EPA/DHA) per gram	5–10%
Decrease carbohydrates: 1% Energy replacement with MUFA/PUFA	1–2%
Each 1% replacement of trans fatty acids for MUFA or PUFA	1%

Adapted from Miller M, et al. (2).

Table 2.

Content of selected Marine-derived sources of Omega-3s (EPA and DHA)

	EPA (mg/100 g)	DHA (mg/100 g)	EPA + DHA (mg/100 g)
Anchovy	763	1292	2055
Herring, Atlantic	909	1105	2014
Salmon, farmed	862	1104	1966
Salmon, wild	411	1429	1840
Mackerel, Atlantic	504	699	1203
Bluefish	323	665	988
Sardines, Atlantic	473	509	982
Trout	259	677	936
Tuna, white (albacore)	233	629	862
Mussels	276	506	782
Striped bass	169	585	754

Adapted from Mozaffaraian D, and Wu J. (15).