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Review

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Effects of Consumption of Various Fatty Acids on Serum HDL-Cholesterol Levels

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Abstract

Since HDL is an anti-atherogenic lipoprotein which plays a role in reversing cholesterol transport from the peripheral tissues to the liver, low HDL-cholesterol (HDL-C) levels are associated with the development of cardiovascular diseases. We previously studied effects of intake of various dietary fat on serum HDL-C levels to make "Dietary Reference Intakes for Japanese 2015", and found that the substitution of fatty acids (FAs) for carbohydrates is beneficially associated with HDL-C, monounsaturated FA (MUFA) intake may not affect HDL-C and trans FA (TFA) is significantly associated with reduction of HDL-C. Consumption of n-3 poly-unsaturated FA (PUFA) was favorably associated with HDL-C. Here we review meta-analyses on the effects of various FA consumption on serum HDL-C levels, to make "Dietary Reference Intakes for Japanese 2020". Consumption of ruminant-TFA may not affect HDL; however, increased industrially produced TFA intake was associated with a significant decrease in HDL and a significant increase in LDL. An intake of n-3 PUFA and MUFA was associated with an increase of HDL. An intake of saturated FA (SFA) was associated with an increase of HDL; however, SFA was also associated with an increase of LDL.

Keywords: High-density lipoprotein; Monounsaturated fatty acids, Poly-unsaturated fatty acids; Saturated fatty acids; Trans fatty acids

Introduction

Atherogenic dyslipidemia is characterized as elevated serum levels of triglyceride (TG) and low-density lipoprotein-cholesterol (LDL-C), and low serum levels of high-density lipoprotein-cholesterol (HDL-C). Since HDL is an anti-atherogenic lipoprotein which plays a role in reversing cholesterol transport from the peripheral tissues to the liver, low HDL-C levels are associated with the development of coronary heart diseases (CHDs) [1, 2], and all-cause mortality [3].

We previously studied effects of intake of various dietary fat on serum HDL-C levels to make "Dietary Reference Intakes for Japanese 2015", by using meta-analyses of clinical trials which evaluated effects of various dietary fat consumption on HDL-C [4]. We found that the substitution of fatty acids (FAs) for carbohydrates is beneficially associated with HDL metabolism, monounsaturated FA (MUFA) intake may not affect HDL-C and trans FA (TFA) is significantly associated with reduction of HDL-C. Consumption of n-3 poly-unsaturated fatty acids (PUFA), especially docosahexaenoic acid (DHA) consumption, was favorably associated with HDL metabolism.

Here we review meta-analyses on the effects of various FA consumption on serum HDL-C levels, to make "Dietary Reference Intakes for Japanese 2020".

Materials and Methods

To make "Dietary Reference Intakes for Japanese 2020", we searched meta-analyses of randomized controlled trial (RCT). A search was conducted by using PubMed, Embase and Google Scholar, with the following keywords: trans FA (TFA) and HDL and meta-analysis or saturated FA (SFA) and HDL and meta-analysis or MUFA and HDL and meta-analysis. The search period was comprised from 2012 up to July 2018.

Results

Meta-analyses which evaluated effects of various FA consumption on HDL-C were shown in Table 1.

Palm oil, SFA

Compared with most other vegetable oils such as olive and sunflower oils, palm oil contains a high amount of SFA (40-50% of total fat) with the majority being in the form of palmitic acid (16:0). Palm oil consumption significantly increased LDL-C compared with vegetable oils low in SFA [5]. Further, palm oil increased HDL-C by 0.02 mmol/L compared with vegetable oils low in SFA and by 0.09 mmol/L compared with TFA-containing oils.

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Table 1. Meta-Analyses Which Evaluated Effects of Various Fatty Acid Consumption on HDL-C

Authors	Assessed studies	Subjects studied	Effects on HDL-C	Effects on other lipids and metabolic parameters
Sun et al [5]	RCTs of at least 2-week duration that compared the effects of palm oil consumption with any of the predefined comparison oils: vegetable oils low in SFA, TFA-containing partially hydrogenated vegetable oils, and animal fats	NA	Palm oil increased HDL-C by 0.02 mmol/L (95% CI: 0.01, 0.04 mmol/L) compared with vegetable oils low in SFA and by 0.09 mmol/L (95% CI: 0.06, 0.11 mmol/L) compared with TFA-containing oils	Palm oil significantly increased LDL-C by 0.24 mmol/L (95% CI: 0.13, 0.35 mmol/L) compared with vegetable oils low in SFA
Gayet-Boyer et al [6]	RCTs to assess the impact of ruminant-TFA (R-TFA) intake on changes in TC/HDL-C ratio	13 RCTs were included, yielding a total of 23 independent experimental groups of subjects	R-TFA did not influence the changes in the ratios of TC/ HDL-C and LDL-C/HDL-C	R-TFA did not influence the changes in the ratios of TC/HDL-C and LDL-C/HDL-C
Fattore et al [7]	Studies included original data comparing palm oil-rich diets with other fat-rich diets and analyzed at least one of the following biomarkers: TC, LDL-C, HDL-C, TC/HDL-C, LDL-C/ HDL-C, TG, apolipoprotein A-I and B, very-low-density lipoprotein cholesterol and lipoprotein(a)	51 studies were included. Intervention times ranged from 2 to 16 week, and different fat substitutions ranged from 4% to 43%	Comparison of palm oil diets with diets rich in stearic acid, MUFA and PUFA showed significantly higher HDL-C and apolipoprotein A-I. Comparison of palm oil-rich diets with diets rich in TFA showed significantly higher HDL-C and apolipoprotein A-I	Comparison of palm oil diets with diets rich in stearic acid, MUFA and PUFA showed significantly higher TC, LDL-C and apolipoprotein B, whereas most of the same biomarkers were significantly lower when compared with diets rich in myristic/lauric acid. Comparison of palm oil-rich diets with diets rich in TFA showed significantly lower apolipoprotein B, TG and TC/HDL-C
Aronis et al [8]	RCTs that examined the role of TFA intake on glucose homeostasis	7 RCTs were included	Increased TFA intake led to a significant decrease in HDL-C (-0.25 mmol/L (95% CI: -0.48 to -0.01))	Increased TFA intake did not result in significant changes in glucose or insulin concentrations. Increased TFA intake led to a significant increase in TC (0.28 mmol/L (0.04 - 0.51)) and LDL-C (0.36 mmol/L (0.13 - 0.60))
Hannon et al [9]	The evidence of the effect of SFA replacement with UFA in metabolically healthy adults with overweight and obesity on dyslipidemia and body composition	8 RCTs enrolling 663 participants were included, with intervention durations between 4 and 28 weeks	NA	Although non-significant (P = 0.06), meta-analysis found UFA replacement to reduce TC by 10.68 mg/ dL (95% CI: -21.90 - 0.53). Reductions in LDL-C and TG were statistically non-significant
Zhang et al [10]	Evidence for the efficacy of n-3 PUFA in managing overweight and obesity	A total of 11 RCTs involving 617 participants were included	There was no significant effect on HDL-C	A statistically non-significant difference was revealed in weight loss between n-3 PUFA and placebo, whereas n-3 PUFA was superior to placebo in reducing serum TG (P = 0.0007; WMD: -0.59; 95% CI: -0.93 to -0.25). A significant reduction in waist circumference (P = 0.005; WMD: -0.53; 95% CI: -0.90 to -0.16) was observed. There were no significant effects on BMI, LDL-C and fasting glucose levels
Xu et al [11]	RCTs focused on serum lipids and inflammatory markers in patients with ESRD. MDs were used to measure the effect of n-3 PUFA supplementation on parameters	20 RCTs involving 1,461 patients with ESRD	n-3 PUFA had no significant effect on HDL-C	n-3 PUFA supplementation reduced TG by 0.61 mmol/L, LDL by 0.35 mmol/L and CRP by 0.56 mmol/L. However, n-3 PUFA had no significant effect on TC, glucose and lipoprotein(a)
Perna et al. [12]	RCTs to estimate the pooled effect of hazelnuts on blood lipids and body weight	9 studies representing 425 participants were included. The intervention diet lasted 28 - 84 days with a dosage of hazelnuts ranging from 29 to 69 g/day	HDL-C remained substantially stable (MD = 0.002 mmol/L)	A significant reduction in LDL-C (MD = -0.150 mmol/L) in favor of a hazelnut-enriched diet was observed. TC showed a marked trend toward a decrease (MD = -0.127 mmol/L). No effects on TG and BMI were found
He et al [13]	RCTs of n-3 PUFA treatment for NAFLD	7 RCTs involving 442 patients (227 for the experimental group and 215 for the control group)	Beneficial changes in HDL-C (6.97 mg/dL (2.05 - 11.90), P = 0.006) favored n-3 PUFA treatment	Beneficial changes in TC (-13.41 mg/dL (-21.44 to -5.38), P = 0.001), TG mg/dl (-43.96 (-51.21 to -36.71), P < 0.00001) favored n-3 PUFA treatment. n-3 PUFA tended towards a beneficial effect on LDL-C (-7.13 mg/dL (-14.26 to 0.0), P = 0.05)
Lu et al [14]	RCTs on the effects of n-3 PUFA in patients with NAFLD	577 cases of NAFLD/NASH in 10 RCTs were included	n-3 PUFA improved HDL in patients with NAFLD/NASH	No significant effects on ALT, AST, TC and LDL. n-3 PUFA improved liver fat, GGT and TG in patients with NAFLD/NASH

Table 1. Meta-Analyses Which Evaluated Effects of Various Fatty Acid Consumption on HDL-C - *(continued)*

Authors	Assessed studies	Subjects studied	Effects on HDL-C	Effects on other lipids and metabolic parameters
Qian et al [15]	Comparing diets high in cis-MUFA to diets high carbohydrates or in PUFA on metabolic risk factors in patients with type 2 diabetes	24 studies totaling 1,460 participants comparing high-MUFA to high-carbohydrate diets and 4 studies totaling 44 participants comparing high-MUFA to high-PUFA diets	When comparing high-MUFA to high-carbohydrate diets, there were significant increases in HDL-C (0.06 mmol/L (0.02 - 0.10))	When comparing high-MUFA to high-carbohydrate diets, there were significant reductions in fasting plasma glucose (-0.57 mmol/L (95% CI: -0.76 to -0.39)), TG (-0.31 mmol/L (-0.44 to -0.18)), body weight (-1.56 kg (-2.89, -0.23)) and systolic blood pressure (-2.31 mm Hg (-4.13, -0.49)). When high-MUFA diets were compared with high-PUFA diets, there was a significant reduction in fasting plasma glucose (-0.87 mmol/L (-1.67 to -0.07))
Khalesi et al [16]	The evidence which identifies the effects of sesame consumption on blood lipid profiles	10 RCTs were identified based on the eligibility criteria	Consumption of sesame did not significantly change HDL-C (0.01 mmol/L; 95% CI: -0.00 - 0.02; P = 0.16)	Consumption of sesame did not significantly change TC and LDL-C. A significant reduction was observed in serum TG (-0.24 mmol/L; 95% CI: -0.32 to -0.15; P < 0.001) after consumption of sesame
Derakhshande-Rishehri, et al [17]	The association of foods enriched in CLA with serum lipid profile in human studies	Healthy adult population	Foods enriched with CLA were associated with non-significantly increased HDL-C (+0.075 mmol/L; 95% CI: 0.121 - 0.270; P = 0.455)	Foods enriched with CLA were associated with significantly decreased LDL-C (-0.231 mmol/L; 95% CI: -0.438 to -0.024; P = 0.028), non-significantly decreased TC (-0.158 mmol/L; 95% CI: -0.349 - 0.042; P = 0.124) and non-significantly decreased TG (-0.078 mmol/L; 95% CI: -0.274 - 0.117; P = 0.433)
Schwingshackl et al [18]	RCTs assessing the long-term effects of low-fat diets compared with diets with high amounts of fat on blood lipid levels	32 studies were included	Rise in HDL-C (+2.35 mg/dL, 95% CI: 1.29 - 3.42; P < 0.0001) was more distinct in the high-fat diet groups. Meta-regression revealed that increases in HDL-C were related to higher amounts of total fat largely derived from MUFA in high-fat diets	Decreases in TC (-4.55 mg/dL, 95% CI: -8.03 to -1.07; P = 0.01) and LDL-C (-3.11 mg/dL, 95% CI: -4.51 to -1.71; P < 0.0001) were significantly more pronounced following low-fat diets, whereas reduction in TG (-8.38 mg/dL, 95% CI: -13.50 to -3.25; P = 0.001) was more distinct in the high-fat diet groups. Meta-regression revealed that lower TC was associated with lower intakes of SFA and higher intakes of PUFA, whereas increases in TG were associated with higher intakes of carbohydrates
Sanders [19]	NA	NA	Compared with carbohydrates, C12-C16 SFAs raise HDL-C without affecting the TC/HDL-C ratio. Replacing 3% dietary SFA with MUFA or PUFA lowers TC/HDL-C ratio by 0.03	Compared with carbohydrates, C12-C16 SFA raises TC, LDL-C without affecting the TC/HDL-C ratio; other SFAs have neutral effects on serum lipids. Replacing 3% dietary SFA with MUFA or PUFA lowers LDL-C by 2% and TC/HDL-C ratio by 0.03
Schwingshackl et al [20]	RCTs and cohort studies investigating the effects of MUFA on cardiovascular and diabetic risk factors	17 relevant papers were identified	Several studies indicated an increase of HDL-C following a MUFA-rich diet	Several studies indicated a decrease in TG following a MUFA-rich diet. The effects on TC and LDL-C appeared not consistent, but no detrimental effects on blood lipids were observed. In type 2 diabetic subjects, MUFA exerted a hypoglycemic effect and reduced glycosylated hemoglobin in the long term
Pei et al [21]	The lipid-modulating effects of n-3 PUFA by combining evidences from RCTs including patients with ESRD	10 RCTs including 557 patients with ESRD	Consumption of n-3 PUFA elevated HDL-C by 0.25 mmol/L, but this change was not statistically significant	Pooled analysis revealed that n-3 PUFA intake significantly reduced serum TG by -0.78 mmol/L (95% CI: -1.12 to -0.44, P < 0.0001). Consumption of n-3 PUFA reduced LDL-C by -0.09 mmol/L, but this change was not statistically significant
Huth et al [22]	The published research on the relationship between milk fat containing dairy foods and cardiovascular health	NA	A diet higher in SFA from whole milk and butter may increase HDL-C and therefore might not affect or even lower theTC/HDL-C	A diet higher in SFA from whole milk and butter increases LDL-C when substituted for carbohydrates or UFA. Cheese intake lowers LDL-C compared with butter of equal milk fat content

CI: confidence interval; CLA: conjugated linoleic acid; ESRD: end-stage renal disease; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density-cholesterol; MD: mean difference; MUFA: mono-unsaturated fatty acid; NA: not available; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PUFA: poly-unsaturated fatty acid; RCT: randomized controlled trial; SFA: saturated fatty acid; TC: total cholesterol; TFA: trans fatty acid; TG: triglyceride; UFA: unsaturated fatty acid.

In another meta-analysis of palm oil on serum lipids, comparison of palm oil diets with diets rich in stearic acid which is a long chain (C18:0) dietary SFA, MUFA and PUFA showed significantly higher HDL-C and apolipoprotein A-I [7]. Comparison of palm oil-rich diets with diets rich in TFA showed significantly higher concentrations of HDL-C and apolipoprotein A-I.

Compared with carbohydrates, C12-C16 SFAs raise serum LDL-C and HDL-C without affecting the TC/HDL-C ratio; other SFAs have neutral effects on serum lipid profile [19]. Results from short-term intervention studies on serum lipids have indicated that a diet higher in SFA from whole milk and butter increases LDL-C when substituted for carbohydrates or unsaturated FA (UFA); however, they may also increase HDL-C and therefore might not affect or even lower the TC/HDL-C ratio [22].

TFA

Since the 1990s, TFAs have been reported to link to harmful effects, as they induce not only an increase in LDL-C but also a decrease in HDL-C [23]. The generic term of TFA represents two independent dietary sources, i.e. an industrial one (industrially produced TFA; IP-TFA) and a natural counterpart (ruminant TFA; R-TFA). R-TFAs are generally present in food at low levels (up to 8% of total FA in milk fat), whereas IP-TFA may reach up to 61% of total FA in pastries and shortenings [24]. R-TFA includes vaccenic acid and conjugated linoleic acid (CLA) that are synthesized by rumen bacteria via the metabolism of MUFA and PUFA [25-27].

The meta-analysis of R-TFA on serum lipids showed that doses of R-TFA did not influence the changes in the ratios of plasma TC/HDL-C and LDL-C/HDL-C [6]. Foods enriched with CLA were associated with a non-significant increase of HDL-C [17]. The meta-analysis showed that increased TFA (IP-TFA) intake led to a significant increase in LDL-C and a significant decrease in HDL-C [8].

n-3 PUFA

In the meta-analysis to evaluate evidence for the efficacy of n-3 PUFA in managing overweight and obesity, a significant reduction in waist circumference was obtained; however, a significant effect of n-3 PUFA on HDL-C was not observed [10]. The meta-analysis of n-3 PUFA on serum lipids in patients with end-stage renal disease (ESRD) also failed to prove a statistically significant beneficial effect of n-3 PUFA on HDL [11, 21]. However, two meta-analyses to identify the effectiveness of n-3 PUFA in non-alcoholic fatty liver disease (NAFLD) showed that n-3 PUFA improved HDL metabolism [13, 14].

Hazelnuts, sesame, MUFA

Hazelnuts are rich in MUFA and antioxidant bioactive substance. The meta-analysis of effect of hazelnuts on blood lipids did not show a significant effect of hazelnuts on HDL [12].

Sesame contains considerable amounts of vitamin E, MUFA, dietary fiber and lignans, which are thought to be associated with its plasma lipid-lowering properties. Consumption of sesame did not significantly change HDL-C [16].

When comparing high-MUFA to high-carbohydrate diets, there were significant increases in HDL-C [15]. Rise in HDL-C was more distinct in the high-fat diet groups, and meta-regression revealed that increases in HDL-C were related to higher amounts of total fat largely derived from MUFA in high-fat diets [18].

According to the synopsis of the evidence available from systematic reviews and meta-analyses using RCTs and cohort studies investigating the effects of MUFA on cardiovascular and diabetic risk factors, several studies indicated an increase of HDL-C following a MUFA-rich diet [20].

Discussion

To make "Dietary Reference Intakes for Japanese 2015", we studied effects of intake of various dietary fat on serum HDL-C levels, by using meta-analyses of RCTs which have been published up to 2012 [4]. In our previous report, the substitution of FA for carbohydrates is beneficially associated with HDL-C, and MUFA intake may not affect HDL-C [4]. However, the present study showed high-MUFA diet significantly increased HDL-C as compared with high-carbohydrates diets [15, 18], and found that several studies indicated an increase of HDL-C following a MUFA-rich diet [20].

We previously reported that TFA is significantly associated with reduction of HDL-C, and that TFA is also adversely related with TC/HDL-C [4]. In the present study, we studied the influences of IP-TFA and R-TFA including CLA on HDL. Interestingly, R-TFA did not influence the changes in the ratios of plasma TC/HDL-C and LDL-C/HDL-C [6], and foods enriched with CLA were associated with a non-significant increase of HDL-C [17]. IP-TFA intake led to a significant increase in LDL-C and a significant decrease in HDL-C [8]. When considering the influence of TFA on serum lipid, it was suggested that IP-TFA and R-TFA have to be considered separately.

Our previous study suggested that n-3 PUFA consumption, especially DHA consumption, may be favorably associated with HDL metabolism [4]. The present study showed that n-3 PUFA did not increase HDL-C in patients with obesity and ESRD [10, 11, 21]; however, n-3 PUFA significantly increased HDL in patients with NAFLD [13, 14]. This result indicates that the effect of n-3 PUFA on HDL-C varies by the difference of clinical backgrounds of studied patients. Our recent study reported that DHA induces a greater increase of HDL-C as compared with eicosapentaenoic acid (EPA) [28], supporting our previous study.

In this study, we also examined the influence of SFA intake on HDL. Palm oil consumption increased HDL-C compared with vegetable oils low in SFA; however, palm oil increased LDL-C [5]. Comparison of palm oil diets with diets rich in stearic acid, MUFA and PUFA showed significantly higher

Table 2. Summary of Effects of Various Fatty Acids Consumption on Serum Lipids

	HDL-C	LDL-C	TG
SFA	↑	↑	
TFA			
Industrially produced-TFA	↓	↑	
Ruminant-TFA	→	→	
CLA (ruminant-TFA)	→	↓	→
n-3 PUFA	→ or ↑	→ or ↓	↓
MUFA	→ or ↑	↓ or →	→ or ↓

CLA: conjugated linoleic acid; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density-cholesterol; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid; TFA: trans fatty acid; TG: triglyceride.

HDL-C and apolipoprotein A-I; however, showed significantly higher LDL-C and apolipoprotein B [7]. Compared with carbohydrates, C12-C16 SFAs raise LDL-C and HDL-C without affecting the TC/HDL-C ratio; other SFAs have neutral effects on serum lipid profile [19]. Replacing 3% dietary SFA with MUFA or PUFA lowers LDL-C by 2% and TC/HDL-C ratio [19]. Both elevation of LDL-C and reduction of HDL-C are very crucial determinants for atherogenesis. Meta-analyses of prospective cohort studies reported the relative risks (95% CI) of high versus low intakes of SFA to be 1.07 (95% CI: 0.96 - 1.19) for CHD, which was not statistically significant [29]. Meta-analysis of RCTs reports mean reductions of 14% (95% CI: 4 - 23) in CHD incidence and 6% (95% CI: -25 - 4; non-significance) in mortality, where SFA was lowered by decreasing and/or modifying dietary fat [30].

The systematic review and meta-analysis which analyzed the associations between intake of SFA and TFA and all-cause mortality, cardiovascular disease (CVD) and associated mortality, CHD and associated mortality, ischemic stroke and type 2 diabetes, was reported [31]. SFA intake was not associated with all-cause mortality (relative risk: 0.99, 95% CI: 0.91 - 1.09), CVD mortality (0.97, 0.84 - 1.12), total CHD (1.06, 0.95 - 1.17), ischemic stroke (1.02, 0.90 - 1.15) or type 2 diabetes (0.95, 0.88 - 1.03) [31]. TFA intake was associated with all-cause mortality (1.34, 1.16 - 1.56), CHD mortality (1.28, 1.09 - 1.50) and total CHD (1.21, 1.10 - 1.33), but not ischemic stroke (1.07, 0.88 - 1.28) or type 2 diabetes (1.10, 0.95 - 1.27) [31]. Industrial, but not ruminant, TFAs were associated with CHD mortality (1.18, 1.04 - 1.33) and CHD (1.42, 1.05 - 1.92) [31].

Conclusions

Summary of effects of various FA consumption on serum lipids was shown in Table 2. Consumption of ruminant-TFA including CLA may not affect HDL-C, and an intake of n-3 PUFA and MUFA was associated with an increase of HDL-C. These FAs may not induce atherosclerosis even by considering the effects of such FA on other serum lipids. The effect of SFA on atherosclerosis has to be carefully considered by accumulation of the effect of HDL-C/LDL-C ratio on CV events. Judging from effect on CV events and serum lipids, IP-TFA consumption may induce atherosclerosis.

Conflict of Interest

The authors declare that they have no competing interests.

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