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Randomized Control Trials

Effects of exchanging carbohydrate or monounsaturated fat with saturated fat on inflammatory and thrombogenic responses in subjects with abdominal obesity: A randomized controlled trial

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SUMMARY

Background & aims: Modification of the amount and type of dietary fat has diverse effects on cardiovascular risk.
Methods: We recruited 54 abdominally obese subjects to participate in a prospective cross-over design, single-blind trial comparing isocaloric 2000 kcal MUFA or carbohydrate-enriched diet with SFA-enriched diet (control). The control diet consisted of 15E% protein, 53E% carbohydrate and 32E% fat (12E% SFA, 13E% MUFA). A total of ~7E% of MUFA or refined carbohydrate was exchanged with SFA in the MUFA-rich and carbohydrate-rich diets respectively for 6-weeks. Blood samples were collected at fasting upon trial commencement and at week-5 and 6 of each dietary-intervention phase to measure levels of cytokines (IL-6, IL-1β), C-reactive protein (CRP), thrombogenic markers (E-selectin, PAI-1, D-dimer) and lipid subfractions. Radial pulse wave analysis and a 6-h postprandial mixed meal challenge were carried out at week-6 of each dietary intervention. Blood samples were collected at fasting, 15 and 30 min and hourly intervals thereafter till 6 h after a mixed meal challenge (muffin and milkshake) with SFA or MUFA (872.5 kcal, 50 g fat, 88 g carbohydrates) or CARB (881.3 kcal, 20 g fat, 158 g carbohydrates)- enrichment corresponding to the background diets.
Results: No significant differences in fasting inflammatory and thrombogenic factors were noted between diets ($P > 0.05$). CARB meal was found to increase plasma IL-6 whereas MUFA meal elevated plasma D-dimer postprandially compared with SAFA meal ($P < 0.05$). Comparing the 3 meals, there were similar postprandial elevations in IL-6 and D-dimer and postprandial reductions in PAI-1, augmentation index and pressure (time effect: $P < 0.05$). CARB diet was found to reduce HDL_3 by 7.8% and increase small dense HDL (sdHDL) by 8.6% compared with SFA diet ($P < 0.05$). SFA diet increased large HDL subfractions compared with both CARB and MUFA diets by 4.9% and 6.6% ($P < 0.05$), respectively.
Conclusions: Overall, the evidence presented in this study suggests that the replacement of SFA with MUFA or refined carbohydrates may not improve inflammatory and thrombogenic markers in abdominally overweight individuals. Indeed increased refined carbohydrates consumption adversely impacts fasting HDL subfractions.
This trial was registered under ClinicalTrials.gov. Identifier no. NCT01665482.

1. Introduction

Obesity is a major health concern, central obesity is of more clinical relevance and related to a cluster of metabolic disorders. Central obesity predisposes to a higher risk of developing cardiovascular diseases, which is related to early onset of pro-inflammatory and pro-thrombogenic states. Studies have reported higher levels of interleukin-6 (IL-6) and plasminogen inhibitor activator-1 (PAI-1) in abdominally obese individuals [1–3]. The accumulation of adipocytes in the abdominal region triggers the release of an array of fat soluble cytokines [4]. The consumption of high fat diets is thought to increase body weight and abdominal fat

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Abbreviations

IL-6	interleukin-6
PAI-I	plasminogen inhibitor activator-1
SFA	saturated fatty acid
CRP	C-reactive protein
MUFA	monounsaturated fatty acid
IL-1β	Interleukin-1β
MPOB	Malaysian Palm Oil Board
sdHDL	small dense HDL
iAUC	incremental area under the curve

deposition, with saturated fatty acid (SFA) considered the chief culprit [5]. In vivo animal data suggest that SFA in particular palmitic acid increase cytokines e.g. IL-6 and interleukin-1. SFA and *trans* fatty acids have been reported to increase C-reactive protein (CRP) [6] but limited data is available to support this. The recommendation to reduce the intake of SFA by replacing with monounsaturated fatty acid (MUFA) or complex carbohydrates has been proposed by the World Health Organisation [7] and other regulatory parties [8,9] based on the impact of SFA on the lipid profile. Data on other clinically relevant metabolic risk biomarkers however is scarce, in particular in populations at high risk of developing cardiovascular disease. The replacement of SFA with carbohydrates has received much debate as increased refined carbohydrates rather than complex carbohydrates intake has been reported to be linked with impaired insulin sensitivity and inflammatory states [10–13].

In order to prevent the possible exposure to cardiovascular disease risk in centrally overweight individuals, who comprise 50% of the population in both Western and Asian countries, determining the best dietary macronutrient composition with least negative metabolic and vascular impact is critical. Therefore, we set out to investigate the effect of replacement of SFA with MUFA or refined carbohydrates on subclinical inflammation, the thrombogenic state, as well as lipid subfractions in centrally overweight subjects who are at risk of developing cardiovascular disease.

2. Materials and methods

2.1. Subjects

The study was approved by the Medical Ethics Committee of University Malaya Medical Centre, Kuala Lumpur, Malaysia (reference no.: 871.5) and registered at ClinicalTrial.gov (Identifier: NCT01665482). Of 54 abdominally overweight subjects recruited, 47 completed the study. Abdominally obese males and females (waist circumference >90 cm for male, >80 cm for female), age 20–60 y were included. Subjects with a medical history of cardiovascular disease, diabetes, dyslipidemia; current use of antihypertensive or lipid lowering medication; plasma cholesterol >6.5 mmol/L, triacylglycerol [14] >4.5 mmol/L; alcohol intake exceeding a moderate intake (>28 units per week); pregnancy, smoker and breastfeeding were excluded.

2.2. Study design

This was a prospective cross-over design, single-blind trial comparing isocaloric 2000 kcal/day MUFA or CARB-enriched diet with SFA-enriched diet (control). The control SFA-enriched diet consisted of 15E% protein, 53E% CARB and 32E% fat (12E% SFA, 13E% MUFA). A total of ~7E% of MUFA or CARB was exchanged with SFA in the MUFA-rich and CARB-rich diets respectively for 6-weeks. Subjects were blinded and randomly allocated to 3 consecutive 6-week dietary treatments using an orthogonal allocation process (ABC, BCA, CAB) using Excel software. At any timepoint, each treatment was allocated 18 subjects with equal gender distribution. Blood samples were collected at baseline (prior to the commencement of study intervention), week 5 and 6. A postprandial mixed meal challenge was conducted at week 6 of each dietary treatment where hourly blood samples collection was done after test meal consumption. Radial pulse wave analysis was measured at baseline and week-6 of each intervention (before meal and 4 h after meal during mixed meal challenge). Fasting plasma IL-6 was the primary outcome of the present study. Secondary outcomes were interleukin-1β (IL-1β), CRP, E-selectin, PAI-1, D-dimer, lipid subfractions and radial pulse wave analyses. The study design is reported in Fig. 1.

2.3. Recruitment methodology

The study intervention was carried out between March and July 2012 at the research institute of Malaysian Palm Oil Board (MPOB). Subjects were recruited via advertisement using posters, internal mail circulation and phone call. Subjects were briefed and provided with a study information brochure. The interested subjects were initially interviewed via a questionnaire over the telephone. Those who met the initial inclusion criteria were invited for a health screening session including medical examination and biochemical profile (glucose, full blood count, lipid profile, kidney and liver function tests). The subjects signed informed consent and provided a 3-day dietary record for the assessment of habitual calorie intake.

2.4. Experimental diets

Habitual dietary intake requirement prior to enrolment was estimated from a 3-day weighed food record using Nutritionist-Pro™ (AXXYA Systems LLC., Stafford, TX, USA). As summarized in Table 1, the experimental diets provided 2000 kcal/day with 55E% carbohydrates, and 32E% fat for both MUFA and SFA diets; a 7E% exchange with fat (in the form of SFA) was applied for CARB diet resulting in a higher carbohydrate and lower fat content compared with the other 2 diets (62E% carbohydrates, 25E% fat). Protein content was standardized across diets at 15E%. Test fats were palm olein IV56 (purchased from MOI Food Malaysia Sdn. Bhd., Malaysia) blended with sunflower oil (purchased from Sunlico®, Yee Lee Edible Oils, Malaysia) for SFA diet, high oleic sunflower oil (purchased from Neuvida®, Yee Lee Edible Oils, Malaysia) blended with sunflower oil for MUFA and CARB diets. 45 g test fat was incorporated into cooking for both SFA and MUFA diets; whereas 34 g fat was incorporated into CARB diet. The sugar sources for CARB diet

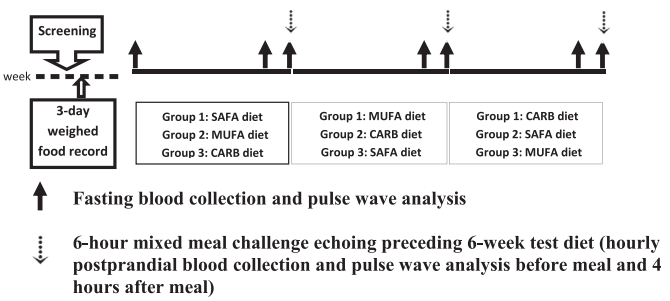

Fig. 1. Study design.

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Table 1
Macronutrient composition of experimental diets and postprandial mixed meals.

	SFA	CARB	MUFA
Experimental diets			
Total calorie (kcal/day)	2054.9 ± 205.7	2081.2 ± 198.1	2054.9 ± 205.7
Total calorie (MJ/day)	8.6 ± 0.9	8.7 ± 0.8	8.6 ± 0.9
Protein (E%)	13.8 ± 2.2	14.3 ± 2.3	13.8 ± 2.2
Carbohydrate (E%)	54.7 ± 4.7	61.4 ± 3.8	54.7 ± 4.7
Dietary sugar (g)[a]	63.2 ± 15.3	91.3 ± 25.7	63.2 ± 15.3
Fat (E%)	31.5 ± 4.3	24.3 ± 2.7	31.5 ± 4.3
SFA (E%)	12.0 ± 0.4	4.5 ± 0.5	5.0 ± 0.8
MUFA (E%)	13.1 ± 0.3	14.0 ± 0.5	20.5 ± 1.0
PUFA (E%)	6.4 ± 0.6	5.8 ± 0.5	6.0 ± 0.5
Dietary fiber (g)[a]	11.3 ± 3.7	12.8 ± 3.7	11.3 ± 3.7
Snacks (cupcake and pancake)			
Total calorie (kcal/day)	128.2 ± 127.8	139.2 ± 131.9	133.2 ± 137.0
Total calorie (MJ/day)	0.5 ± 0.5	0.6 ± 0.6	0.6 ± 0.6
Mixed meals[a]			
Total calorie (kcal)	872.1	881.3	872.1
Total calorie (MJ)	3.7	3.7	3.7
Protein (g)	15.8	15.8	15.8
Carbohydrate (g)	88.0	157.6	88.0
Dietary sugar (g)	56.3	123.2	56.3
Fat (g)	50.7	20.8	50.7
SFA (g)	19.7	1.5	3.7
MUFA (g)	20.6	13.5	36.9
PUFA (g)	9.7	5.0	9.1
Dietary fiber (g)	0.7	0.7	0.7

Mean values ± SD. Duplicates of the meals were collected for total fat (Soxhlet method) and protein content (Kjeldah method).
Abbreviations: E, energy; SFA, saturated fatty acid; CARB, carbohydrate; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
[a] Calculated using Nutritionist Pro™ software (AXXYA Systems LLC. Texas, USA).

were rose syrup, honey and barley drinks which provided 40, 40, 60 g sucrose respectively (mean glycemic index 35.5, glycemic load 21.6). All other food components were identical between diets: breakfast consisting of a serving of refined carbohydrate (fried rice or fried noodles) plus 1 carbohydrate snack, a serving of fruit and a serving of drink; lunch and dinner: a serving of protein source (fish, meat or chicken), 1 serving of carbohydrate-rich foods (rice, noodles, or spaghetti), 1 serving of vegetables and fruits for each meal. Cholesterol intake was limited to <200 mg/day by restricting egg and seafood intake, and only providing lean meat without skin. Subjects were provided three 5-day cycle menus with breakfast and lunch served at the dining hall of research institute, and dinner was packed home.

Additional energy requirement was adjusted using snacks coded to blind the subjects (cupcake with 3 flavors-vanilla, orange and strawberry, and pancakes) containing ~156 kcal with matching nutrient proportion with the background diet. Amount of test fats needed was calculated for everyday cooking and provided to the caterer. Subjects were provided guidelines to prepare meals at home using test cooking oils during weekends and holidays.

2.5. Mixed meal composition

The mixed meal consisted of a high fat (50 g fat) muffin and a strawberry-flavored milkshake (Nesquik® (Nestle, Switzerland)) in the case of subjects on a background SFA/MUFA diet-intervention; additional carbohydrate content in a low fat/high carbohydrate muffin (20 g fat) and a milkshake was supplied by 70 g Valens Caborie® glucose polymers module (Pharm-D, USA) for subjects on a CARB background diet. The high fat challenge meals (for both SFA and MUFA meals) provided 900.8 kcal (3.78 MJ), 90.4 g carbohydrates and 50 g test fats; whereas the low fat/high carbohydrate challenge meal (CARB meal) provided 803.2 kcal (3.73 MJ), 221.3 g carbohydrates and 20 g test fat. The CARB meal utilized 61.6 g sucrose as the main carbohydrate source. The muffins were prepared in batches before the study day and stored in −20 °C freezer. The muffins were heated in the microwave before serving to subjects during study day.

2.6. Mixed meal challenge procedure

On the last day of each 6-week intervention, subjects were provided a low fat chicken-flavored instant cup porridge meal (providing 180 kcal with 1 g fat) for dinner and required to fast after 22:00. The subjects were asked to refrain from strenuous exercise, caffeine and alcohol intake a day before the mixed meal challenge day. On arrival at the center on the morning of the study, subjects filled up a questionnaire to assess activity and food intake a day before. The subject's blood pressure and radial pulse wave analyses were measured using SphygmoCor System (AtCor Medical, Australia). A venous cannula was inserted into the antecubital vein of the forearm to facilitate multiple blood samples. The subject was then served with challenge test meal to consume within 10 min. Subsequent blood samples were collected at 15 min, 30 min, and hourly intervals till 6 h. At 4-h, subject's blood pressure and radial pulse wave analyses were measured again by the same technician. At the end of 6 h, subjects were provided lunch to consume.

2.7. Compliance measures

The attendance and meal intake were closely monitored by a nutritionist. Subjects found skipping meals were monitored closely and those found to miss over 10% of the meals over the course of each 6-week intervention period were considered drop-outs. No subjects were requested to quit the study due to noncompliance based on these criteria. Body weight was monitored bi-weekly and subjects with body weight fluctuations more than 2 kg were advised to adjust calorie intake. Total plasma fatty acid and erythrocyte membrane phospholipid fatty acid composition were analyzed at week 6 of each diet-treatment to monitor subject compliance.

2.8. Fasting blood sample collection

Fasting blood samples were collected at baseline, week 5 and 6 of each dietary treatment. Serum samples for the analyses of triacylglycerol, CRP and lipid profile were collected into tubes siliconized with clot activator. EDTA K3 tubes (1.2–2.0 mg EDTA/1 mL of blood) were used for plasma cytokines and citrated tubes (3.2% or 0.109 mol/l sodium citrate) for thrombogenic markers. All samples were centrifuged at 1529 × *g* for 15 min and stored at −80 °C until analysis. Packed erythrocytes (after plasma removal) were stored at 4 °C and analyzed within 5 days.

2.9. Laboratory analyses

IL-6, IL-1β, and E-selectin were analyzed using Quantikine HS® colorimetric sandwich ELISA (R&D System, USA). The interassay values were 6.4, 10.8, 5.8% respectively, n = 22. PAI-1 was analyzed using IMUBIND® plasma PAI-1 ELISA kit (Sekisui Diagnostics, USA) with interassay values at 7.2%, n = 22. Plasma D-dimer was assayed by IMUCLONE™ D-dimer ELISA kit (Sekisui Diagnostics, USA) (interassay CV% = 3.3%, n = 22). Lipid profile and CRP assay were analyzed by an accredited clinical laboratory (Pathlab & Clinical Laboratory Sdn. Bhd., Malaysia) using ADVIA 2400 Chemistry (Siemens Healthcare Diagnostics Inc., USA). The interassay CV% for total cholesterol, triacylglycerol, apo A-1, apo B-100 and CRP assays were 1.5% (n = 2), 2.6% (n = 2), 1.1% (n = 2), 0% (n = 2), 1.7% (n = 2) respectively (Siemen Healthcare Diagnostics Products Inc., USA). LDL cholesterol was calculated using Friedewald's equation. Radial

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pulse wave analyses were analyzed by SphygmoCor System (AtCor Medical, Australia) by the same technician with intraassay CV at 3.8% (n = 47).

2.10. Statistics

A sample size of 48 subjects was calculated to have 80% power to detect a difference of 0.5 SD unit change of IL-6 at $P = 0.01$. SPSS version 18 (SPSS Inc, Chicago, IL) and GraphPad Prism software version 5.02 (Graph Pad software, Inc., La Jolla, CA, USA) were used for statistical analyses. Data distribution normality was determined and logarithmic transformation conducted for data not normally distributed. Fasting concentrations were tested at week 5 and 6 for any time trends. No time trend was detected and data were averaged and presented as mean/geometric mean ± SEM for fasting measurements or mean/geometric mean (95% CI) for postprandial measurements. Fasting data were analyzed by repeated measure ANOVA; whereas postprandial data were analyzed by one way repeated measure ANOVA, with time and meal as within subject factors and gender as between subject variables. Bonferroni post-hoc test was conducted for comparison between treatments. Incremental area under the curve (iAUC) was calculated for all postprandial data.

3. Results

The characteristics of 47 subjects (35 women, 12 men) who completed the 3 x 6-week dietary intervention are presented in Table 2. 54 subjects fulfilling all inclusion criteria were randomized into three groups: 5 subjects dropped out during the first intervention (2 were unable to commit, 1 had health problems, 2 became pregnant) and 2 dropped out during second intervention (1- health problems, 1- pregnant). 47 subjects completed fasting blood collection and all 3 dietary interventions, 1 subject refused to participate in the postprandial mixed meal challenge and 46 subjects (34 women, 12 men) completed all 3 postprandial mixed meal challenges.

Table 2
Characteristics of study subjects.

	All[b]
Physical characteristics	
Age (y)	32.8 ± 8.7
Gender	
Female (*n*)	35
Male (*n*)	12
Height (m)	159.4 ± 7.8
Weight (kg)	74.2 ± 14.6
BMI (kg/m^2)	28.7 ± 4.1
Waist (cm)	94.8 ± 10.2
Body fat (%)	36.6 ± 7.9
Systolic BP (mmHg)	124.5 ± 12.4
Diastolic BP (mmHg)	81.8 ± 10.7
Aortic augmentation pressure (mmHg)	6.1 ± 4.9
Aortic augmentation index (%)	18.7 ± 12.8
Biochemical profile	
Serum total cholesterol (mmol/L)	5.0 ± 0.8
Serum HDL cholesterol (mmol/L)	1.3 ± 0.3
Serum LDL cholesterol (mmol/L)	3.1 ± 0.7
Serum triacylglycerol (mmol/L)	1.2 ± 0.7
Total: HDL cholesterol	4.0 ± 0.8
Plasma glucose (mmol/L)	5.8 ± 0.8
Plasma IL-6 (pg/ml)[a]	1.4 ± 0.8
Plasma IL-1β (pg/ml)	0.2 ± 0.1
Serum CRP (mg/L)[a]	3.7 ± 4.3
Plasma E-selectin (ng/mL)[a]	36.3 ± 13.5
Plasma PAI-1 (ng/ml)	63.2 ± 31.3
Plasma D-dimer (ng/ml)[a]	254.0 ± 137.6
Dietary intake[c]	
Energy (kcal/day)	2051.8 ± 545.3
Protein (E%)	16.3 ± 2.8
Carbohydrate (E%)	57.3 ± 7.2
Fat (E%)	26.9 ± 6.2

Abbreviations: BP, blood pressure; IL-6, interleukin-6; IL-1β, interleukin-1β; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1.
[a] Means or geometric means ± SD.
[b] Ethnicity: Malay $n = 47$.
[c] Determined from 3-day weighed diet record using Nutritionist Pro™ software (AXXYA Systems LLC. Texas, USA).

3.1. Compliance

Extra energy intake from daily snacks was not significantly different between diet groups (Table 1). Full meal intake was achieved in 97.1 ± 4.4%, 98.0 ± 3.2% and 97.1 ± 5.1% of subjects for SFA, CARB and MUFA diets respectively. The meal appreciation and palatability assessed by VAS (ranging from 0 to 10) were 7.0 ± 1.2, 7.1 ± 1.3, 6.9 ± 1.4 and 7.2 ± 1.3, 7.3 ± 1.3, 7.1 ± 1.4 for SFA, CARB and MUFA diets respectively. Body weight was constant across interventions at weight 73.8 ± 14.4 kg, 73.9 ± 14.6 kg and 73.9 ± 14.3 kg, respectively for SFA, CARB and MUFA diets. Total plasma fatty acid and erythrocyte membrane phospholipid fatty acid composition reflected dietary intake indicating good compliance. Palmitic acid content was higher ($P < 0.05$) after SFA diet (26.8 ± 2.3%) compared with CARB (26.3 ± 1.8%) and MUFA diets (26.0 ± 2.0%). Overall subject compliance was good.

3.2. Fasting metabolic risk markers

Table 3 summarizes fasting measurements for inflammatory and thrombogenic markers. The primary outcome, fasting plasma IL-6 levels were similar after exposure to 6 weeks of SFA, CARB and MUFA diets respectively. Neither were there significant differences in fasting plasma IL-1β, CRP, E-selectin, PAI-1 and D-dimer between the 3 diets after 6 weeks of exposure.

The results of fasting lipids after each dietary intervention are profiled in Table 4. As expected, MUFA diet resulted in a slightly lower total cholesterol level and LDL cholesterol level compared with SFA diet $P < 0.05$). CARB diet was associated with lower HDL cholesterol level compared with SFA diet ($P < 0.05$). No difference was observed between diets in total: HDL cholesterol ratio, VLDL cholesterol, apo A-1, apo B-100, lp(a) and TAG levels. Interestingly, CARB diet resulted in lower HDL_3 subfraction and higher small dense HDL (sdHDL) subfraction compared with SFA diet ($P < 0.05$). SFA diet increased large HDL subfractions compared with both CARB and MUFA diets ($P < 0.05$), respectively.

3.3. Postprandial metabolic responses

The postprandial response of plasma cytokines and thrombogenic markers over 6 h to the mixed meal challenge with macronutrient composition echoing the 3 background diets are shown in Fig. 2, graphs A-F. With all 3 background diets, IL-6 rose after the postprandial challenge. Repeated measure ANOVA did not show significant differences between diets in plasma IL-6 at individual time-points over 6 h (time effect: $P = 0.000$, meal × time interaction: $P = 0.245$). However $iAUC_{0-6\ h}$ IL-6 was 66% higher after CARB challenge compared with SFA challenge ($P < 0.05$). Time ($P = 0.020$) but not meal × time interaction ($P = 0.077$) was observed for plasma IL-1β over 6 h. Plasma IL-1β was found to fall below baseline at 2 h with all 3 meals. Repeated measure ANOVA for E-selectin showed significant meal × time interaction ($P = 0.035$) and a borderline significant value for iAUC between the 3 challenge meals ($P = 0.051$). There was a time trend effect ($P = 0.000$) where PAI-1 levels were reduced 4 h after all 3 challenge meals but no

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Table 3
Fasting inflammatory and thrombogenic variables after following SFA-, CARB- and MUFA diets for 6-week.

	SFA diet	CARB diet	MUFA diet
IL-6 (pg/mL)[a]	1.523 (1.305, 1.740)	1.562 (1.264,1.861)	1.523 (1.305, 1.740)
IL-1β (pg/mL)	0.262 (0.237, 0.286)	0.253 (0.228, 0.277)	0.253 (0.227, 0.279)
CRP (mg/mL)[a]	4.023 (2.819, 5.227)	3.845 (2.572, 5.117)	3.702 (2.624, 4.780)
E-selectin (ng/mL)[a]	36.47 (32.30, 40.73)	36.53 (32.40, 40.83)	36.53 (32.40, 40.65)
PAI-1 (ng/mL)	63.85 (55.88, 71.81)	62.48 (54.90, 70.07)	63.91 (56.16, 71.66)
D-dimer (ng/mL)[a]	245.3 (213.7, 276.8)	260.7 (221.2, 300.0)	257.1 (223.2, 291.0)
Aortic systolic pressure (mmHg)	113.4 (109.6, 117.3)	109.4 (106.4, 112.4)	109.5 (106.4, 112.6)
Aortic diastolic pressure (mmHg)	83.28 (80.17, 86.38)	79.73 (77.18,82.28)	79.38 (76.58,82.17)
Aortic pulse pressure (mmHg)	30.13 (28.24, 32.02)	29.67 (28.06, 31.29)	30.11 (28.51, 31.72)
Aortic augmentation pressure (mmHg)	6.1 (4.8, 7.5)	5.7 (4.5, 6.9)	5.6 (4.5, 6.8)
Aortic augmentation index (%)	18.69 (15.03, 22.35)	18.22 (14.97, 21.46)	17.59 (14.51, 20.67)

Abbreviations: SFA, saturated fatty acid; CARB, carbohydrate; MUFA, monounsaturated fatty acid, IL-6, interleukin-6; IL-1β, interleukin-1β; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1.
[a] Values are means or geometric means with 95% CI. $n = 47$ (women $n = 35$; men $n = 12$) for all 3 dietary interventions, measured at fasting state. Data were analyzed by repeated measures ANOVA among 3 diets.

Table 4
Fasting lipid profile after following SFA-, CARB- and MUFA diets for 6-week.

	SFA diet	CARB diet	MUFA diet
Total cholesterol (mmol/L)	4.89 (4.68, 5.09)	4.79 (4.58, 4.4.99)	4.71 (4.48, 4.94)[b]
LDL cholesterol (mmol/L)	3.05 (2.89, 3.21)	3.00 (2.84, 3.17)	2.89 (2.71, 3.10)[b]
Mean LDL particle size (nm)	270.9 (270.0, 271.9)	270.4 (269.4, 271.3)	270.7 (269.8, 271.5)
Small dense LDL (%)	4.36 (2.87, 5.84)	5.02 (3.38, 6.65)	4.66 (3.24, 6.08)
HDL cholesterol (mmol/L)	1.23 (1.17, 1.29)	1.18 (1.13, 1.24)[b]	1.21 (1.14, 1.28)
HDL-2 (%)	13.62 (12.53, 14.72)	13.09 (12.08, 14.09)	13.06 (12.17,13.95)
HDL-3 (%)	9.42 (8.59, 10.24)	8.74 (7.97, 9.51)[b]	8.95 (8.16, 9.74)
Small HDL particle (%)	11.55 (10.22, 12.88)	12.54 (11.23, 13.85)[b]	12.06 (10.93, 13.19)
Intermediate HDL particle (%)	54.07 (52.55, 55.59)	54.73 (53.35, 56.12)	55.75 (54.25, 57.25)[b]
Large HDL particle (%)	34.17 (31.84, 36.49)	32.58 (30.41, 34.76)[b]	32.07 (30.05, 34.09)[b]
Total: HDL cholesterol	4.06 (3.84, 4.28)	4.13 (3.91, 4.36)	4.01 (3.76, 4.25)
VLDL cholesterol (mmol/L)	0.76 (0.70, 0.82)	0.76 (0.70, 0.82)	0.75 (0.69, 0.82)
Apo B-100 (g/L)	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)	0.90 (0.85, 0.95)
Apo A-1 (g/L)	1.27 (1.22, 1.31)	1.25 (1.21, 1.29)	1.27 (1.22, 1.32)
Apo B-100: apo A-1	0.72 (0.68, 0.77)	0.74 (0.69, 0.79)	0.72 (0.67, 0.77)
Lipoprotein (a) (mg/dL)[a]	16.9 (13.6, 20.2)	17.9 (14.0, 21.7)	17.4 (14.2, 20.7)
Triacylglycerol (mmol/L)[a]	1.34 (1.13, 1.55)	1.32 (1.14, 1.49)	1.34 (1.13, 1.55)

Abbreviations: SFA, saturated fatty acid; CARB, carbohydrate; MUFA, monounsaturated fatty acid; apo B-100, apolipoproteinB100; apo A-1, apolipoproteinA1.
[a] Values are means or geometric means with 95% CI. $n = 47$ (women $n = 35$; men $n = 12$) for all 3 dietary interventions, measured at fasting state. Data were analyzed by repeated measures ANOVA among 3 diets.
[b] Significantly different compared with SFA ($P < 0.05$).

meal × time interaction ($P = 0.348$) was observed. Plasma D-dimer was found to increase after meals (time effect, $P = 0.000$) but meal × time interaction was similar between meals ($P = 0.889$). iAUC showed that MUFA meal increased D-dimer 43% more than SFA over 6 h compared with SFA meal ($P < 0.05$). iAUC did not differ between diets for IL-1β, E-selectin, PAI-1 over 6 h ($P > 0.05$). There was no significant time ($P = 0.358$) and meal x time effect ($P = 0.549$) on serum CRP responses. The 6-h postprandial response and iAUC for serum triacylglycerol are shown in Fig. 2I. There was significant meal × time interaction ($P = 0.002$) based on deviations from baseline. Peak triacylglycerol was at 4 h after all meals, and the iAUC triacylglycerol for CARB meal was lower than that with SFA and MUFA meal ($P < 0.000$).

3.4. Pulse wave analysis

Augmentation index (%) and augmentation pressure as indicators of arterial stiffness were not affected by the three diets at fasting state. The markers were also measured at fasting and at 4 h during mixed meal challenge, there was time trend effect ($P = 0.000$) where the index was decreased after all meals at 4 h (Fig. 2, graphs G & H).

4. Discussion

The present study was designed to investigate the effect of 7E% replacement of SFA with refined CARB or MUFA on cardiovascular-related metabolic risk markers including inflammatory and thrombogenic parameters, and the lipid profile. The primary outcome, fasting plasma IL-6 was not altered by 6 weeks exposure to the three isocaloric diets: SFA (55% carbohydrate, 32% fat- 12% SFA, 13% MUFA), CARB (61% carbohydrate, 25% fat- 5% SFA, 14% MUFA) or MUFA (55% carbohydrate, 33% fat − 5% SFA, 20% MUFA). Neither was there any substantial impact of dietary modification on other cytokines (IL-1β and E-selectin), CRP, and thrombogenic markers (PAI-1 and D-dimer), arterial stiffness (augmentation index) in the fasting state.

Epidemiological studies suggest that elevated fasting CRP and IL-6 are associated with coronary heart disease [7,15]. The present study subjects with central obesity had higher mean concentrations of fasting cytokines, CRP and thrombogenic parameters at baseline compared with normal weight, healthy Asian [16] and Caucasian [17] individuals studied by other groups. The substitution of MUFA or refined CARB for SFA however did not result in improvement of these parameters in the fasting state in this group

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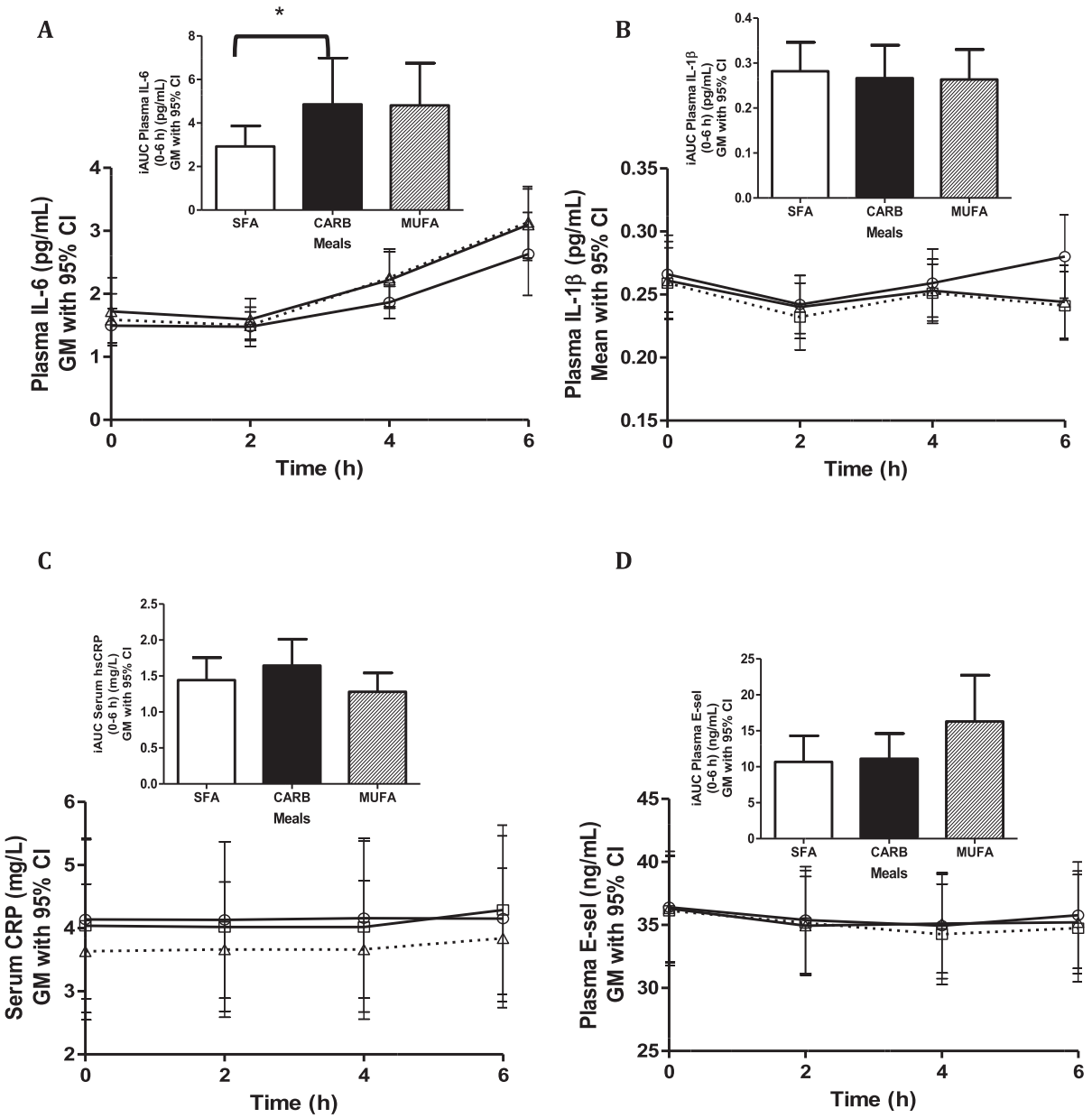

Fig. 2. Postprandial interleukin-6 (IL-6) (A), interleukin-1β (IL-1β) (B), C-reactive protein (CRP) (C), E-selectin (D), plasminogen activator inhibitor-1 (PAI-1) (E), D-dimer (F), augmentation index (G), augmentation pressure (H) and triacylglycerol (I) following mixed meal rich in saturated fatty acid (SFA), carbohydrate (CARB) or monounsaturated fatty acid (MUFA) at the end of each 3 × 6-week dietary intervention. Data are means (B and H) or geometric means (A, C–G and I) with 95% CI, $n = 46$ (34 women, 12 men). White circle, solid line = SFA; white triangle, solid line = CARB; white square, dotted line = MUFA. Repeated measures ANOVA of values from preprandial value (3 meals, 3 time points for A-F, 1 time point for G-H, 6 time points for I) with gender as a between subject factor: meal × time interaction: (A–C, E–H) $P > 0.05$, (D, I) $P < 0.05$; meal × time × gender interaction: (A–I) $P > 0.05$. [6]Significant differences in changes from preprandial value between CARB vs SFA and MUFA (I). *Insert*: Incremental areas under the curve (iAUC) over 6 h (A–F and I) or 4 h (I). Data are geometric means with 95% CI. White bars = SFA; black bars = CARB; striped bars = MUFA. *Significant difference in iAUC between SFA and CARB or MUFA, $P < 0.05$ (A, F and I).

of subjects who are vulnerable to disease progression. In agreement with our findings, Lithander et al. [18] reported that fasting CRP, IL-6 and TNF-α did not differ between a high SFA or low SFA fat diet differing by 5E% fat after a 3-week crossover trial in mildly hyperlipidemic Caucasian subjects. A large scale study in a Caucasian cohort of subjects at risk of developing metabolic syndrome also found that altering the composition of SFA, MUFA coupled with high or low glycemic index diet for a duration of six months did not alter CRP, sICAMs, PAI-1 [19]. In contrast with the aforementioned findings, a study in healthy subjects reported that an oleic acid (MUFA) enriched diet reduced both CRP and IL-6 levels when compared with *trans* fatty acids after a 4-week dietary intervention [6]. Casas et al. [20] reported that Mediterranean diet supplemented with both nuts and extra virgin olive oil (a rich source of MUFA) were found to lower plasma IL-6, CRP, sICAMs and P-selectin compared with a low fat diet after a 1 y long term dietary intervention in subjects at risk of developing cardiovascular diseases. The study suggested that the nutrients in the Mediterranean diet

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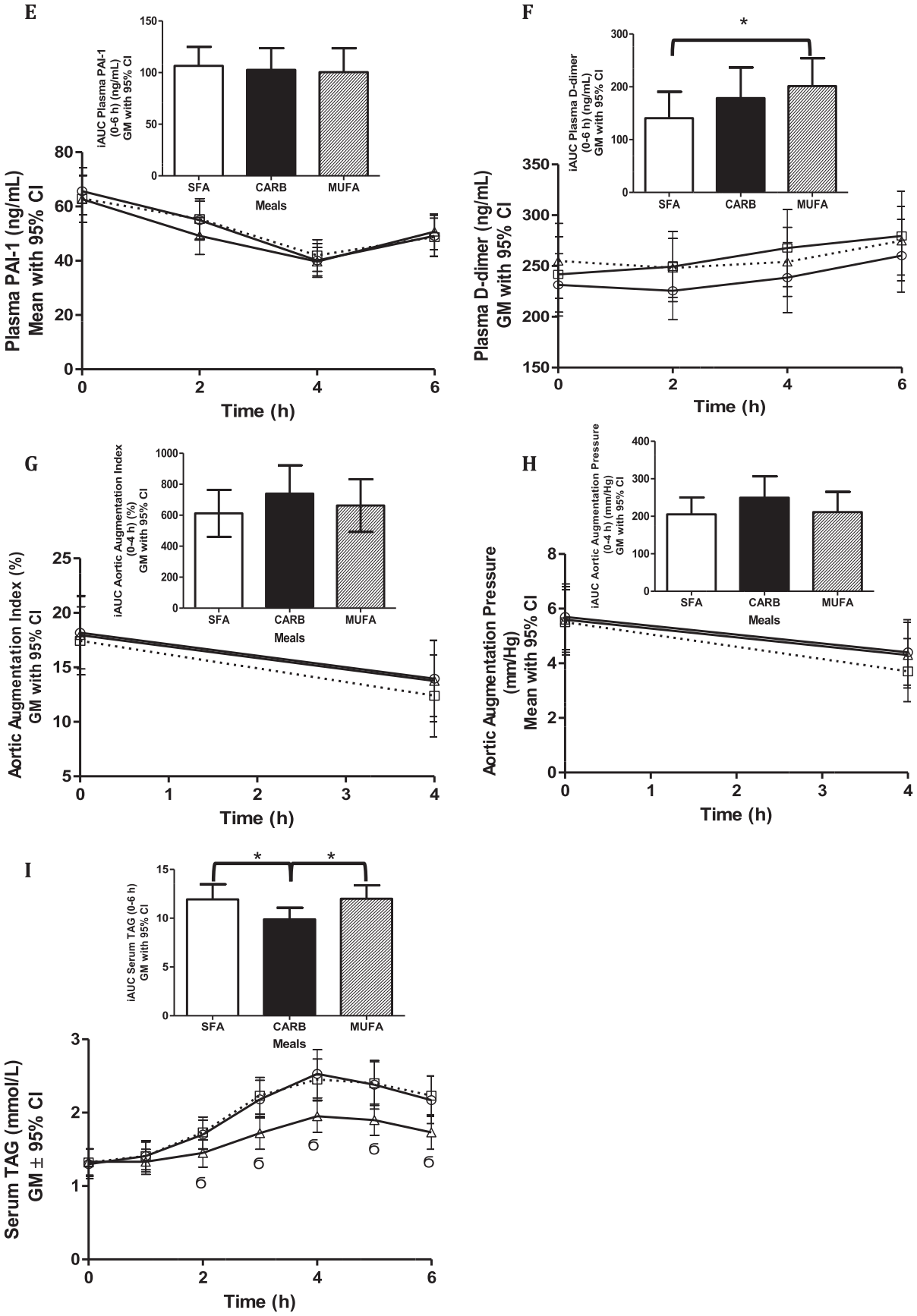

Fig. 2. (*continued*).

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and a long study duration (at 1 y) maybe needed for a pronounced impact of dietary modification on inflammatory biomarkers related to atherosclerosis. A study comparing the supplementation of n-3 PUFA (1100 mg), which is regarded as anti-inflammatory did not improve subclinical inflammation, weight loss of 9.4 kg however significantly bring down the levels of cytokines [21,22]; this has also been reviewed elsewhere [4].

A large scale long term study found that dietary fatty acids at 5E% exchange between SFA, refined carbohydrates and MUFA did not exert significant impact on arterial stiffness and peripheral augmentation index in subjects at high risk of developing metabolic syndrome for a 6-mo intervention [23]. Observational studies report higher sdHDL subfraction and lower large HDL subfractions in the patient groups with the diagnosis of coronary artery disease [24,25]. In addition, HDL_3 may predict lower risk for CHD [25]. The current study did not observe a change in % sdLDL between diets, as reported by other similar studies [19]. The CARB diet (in comparison with the SFA diet) however was associated with lower fasting HDL cholesterol. Lipid subfraction analysis showed that the decrease in HDL was due to a reduction in HDL_3 which was associated with a concommitant increase in % sdHDL when compared with SFA diet ($P < 0.05$). SFA diet on the other hand increased the large HDL subfraction compared with both CARB and MUFA diets ($P < 0.05$), respectively. A study comparing soybean oil (MUFA) and butter (SFA) in hypercholesterolemic Caucasians found no significant difference in HDL-2 and HDL-3 subfractions after a 7-week diet intervention [26]. To our knowledge, no similar studies compared the effects of high-fat and high-carbohydrate in particular refined carbohydrates diets on HDL subfractions. Taken together, our study findings imply that high carbohydrate consumption may increase CAD or CHD risk as compared to high SFA intake as high refined carbohydrate intake is associated with higher sdHDL subfraction, lower large HDL subfraction and lower HDL3.

The influence of dietary modification on postprandial responses is however different. The present study reveals that replacement of SFA with refined CARB in a mixed meal after a similar background diet for 6 weeks elevated postprandial $iAUC_{0-6\ h}$ of IL-6. On the other hand, replacing SFA with MUFA in a high fat snack elevated D-dimer responses but not other parameters measured. PAI-1 and augmentation index were found to decrease from baseline at 4 h after all 3 meal challenges. In our previous published study on the acute effect of mixed meal challenges with similar dietary composition conducted in metabolic syndrome Asian subjects, postprandial IL-1β, CRP and PAI-1 as in the present study were not different between the 3 meals. However unlike our current study (where postprandial IL-6 and D-dimer were higher after MUFA and CARB meal-challenges respectively), in the acute setting without a prior 6-week background diet exposure of similar composition to the mixed meal, both IL-6/D-dimer were not different between the 3 meal-challenges [27]. We expect to observe a more pronounced effect of dietary fat modification in overweight subjects as excess central adipose tissue secretes proinflammatory markers and this population is exposed to increased risk of developing chronic diseases. However, in contrast to our expectations, our findings are in concord with our previous study in healthy Asian subjects that 6 weeks exposure to diets high in SFA or MUFA do not differentially affect IL-6, CRP, TNF-α and IL-1β levels after challenge meals [28]. It has been reported that the ingestion of a minimum of 50 g fat is needed for the detection of postprandial cytokine activation [29]. Previous studies consistently reported that high fat meals triggered inflammatory responses (reviewed by our group [4]) and our study indeed observed postprandial IL-6 elevation with the use of 50 g fat in the SAFA and MUFA challenges. The high refined CARB meal which only contained 20 g fat, increased postprandial IL-6 levels to a greater extent when compared to the high-fat (SAFA) meal. This coupled with the deleterious changes in HDL subfractions after the high refined CARB diet is of significance in the light of controversy about high refined carbohydrate versus high fat diets. Our work seems to indicate that even a short exposure to a high refined CARB diet leads to negative changes in surrogate inflammatory markers and lipid component indicative of increased cardiovascular risk in abdominally overweight Asian subjects. It has also been reported that the optimal time to evaluate changes in CRP in blood plasma is 24 h postprandially and this explains our observations of unchanged CRP levels up to 6 h postprandially [30]. In studies using butter as a dietary SFA source, butter was found to increase cytokines postprandially to a greater extent [31] compared with polyunsaturated fats in obese subjects. One possible explanation might be that the medium chain triglyceride content of butter is more rapidly absorbed compared with that of other SFA sources such as palm oil [32].

It is to be noted that no power calculations were carried out in relation to the postprandial part of the study. There might be chances of statistical type 1 errors due to the high number of statistical analyses performed. The consequence might be that some of the statistical differences are only observed by chance (for example the group differences in iAUC for IL-6 and D-dimer). These results need further confirmation in a larger scale study with power calculation. The strengths of our present dietary intervention study are a standardized supervised well-controlled dietary intake by study participants despite free-living conditions, good compliance of study participants (as reflected by the post-intervention cholesterol profile as predicted by Mensink's equation [33] and the erythrocyte membrane and plasma fatty acid composition), and the long duration of assessment of the postprandial challenge (up to 6 h). Another strength of our study is the higher proportion of complex and refined carbohydrate sources utilized which is reflective of the dietary pattern in South East Asia and perhaps even other Asian populations in India and China. In comparison with the Mediterranean and typical American diets, effects of this carbohydrate-heavy diet in Asian subjects which is consumed by a large proportion of the world's population has not been as well delineated in the literature. However our findings cannot therefore be extrapolated to other populations with diets of differing macronutrient composition. In addition, our findings in high refined carbohydrate diet cannot be related to diets high in complex carbohydrates, which is the diet recommended by WHO.

The findings of the present study suggest that the replacement of SFA with MUFA or refined carbohydrates do not differentially impact fasting inflammatory and thrombogenic markers in abdominally overweight Asian individuals. High refined carbohydrate consumption adversely impact on fasting HDL subfractions in this high-risk group. Further confirmation is needed on the impact of high refined carbohydrates and MUFA on proinflammatory and thrombogenic responses postprandially.

Statement of authorship

KTT: designed the research protocol; conducted the research and statistical analysis; prepared the manuscript and had primary responsibility for final content. LFC: contributed to the planning and management of study, laboratory and data analyses; conducted the research and contributed to manuscript writing. SRV: designed the study and contributed to the manuscript writing. KN, TABS: contributed to critical revision of the manuscript.

Conflict of interest

KTT and KN are employees of the MPOB. LFC was the recipient of Graduate Student Assistantship Scheme (GSAS) scholarship from

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MPOB. TABS is a member of the Programme Advisory Committee of the MPOB. SRV declares no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2016.08.026.

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