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Original Article

Genetic and nutritional interaction: impact of isomaltooligosaccharide and PRKAA2 & ABCA1 polymorphism on Castelli's risk index

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Abstract

Castelli's Risk Index 1 (CRI1) can be used to estimate the risk of developing ischemic heart disease, which can be influenced by hyperlipidemia. Both genetic variants, including ABCA1 rs2066714 and PRKAA2 rs1124900, and also consuming isomaltooligosaccharide (IMO) can affect hyperlipidemia. The study's objectives are to examine the alterations in CRI1 in hyperlipidemia subject who eat IMO cookies and have genetic differences. 30 DNA samples were taken from hyperlipidemic participants who received a 4-week treatment of IMO cookies and a control. Genetic variation analysis using PCR-RFLP and restriction enzymes digestion (AfiIII for PRKAA2 rs1124900 and EcoRV for ABCA1 rs2066714). Consumption of IMO significantly reduced CRI1 (8.06%) in patients with hyperlipidemia ($p<0.05$). Interaction genotypes TG and GG of PRKAA2 rs1124900 with IMO consumption lowering CRI1 ($p<0.05$). In conclusion, consuming IMO cookies can lower the risk of CRI1 in those with TG and GG genotypes of PRKAA2 rs1124900.

Keywords: cardiac index, oligosaccharide, ABCA, PRKAA2, hyperlipidemias

Introduction

Hyperlipidemia is an increase in blood lipids or lipoproteins that is associated with an increased risk of cardiovascular illness such as ischemic heart disease [1–3]. Castelli's Risk Index I (CRI I) can predict the risk of cardiovascular disease caused by changes in blood lipid levels by comparing total cholesterol levels with High Density Lipoprotein (HDL) levels [4, 5]. In Indonesia, the prevalence of elevated total cholesterol is 35.9%, whereas the prevalence of decreased HDL is 22.9% [6]. Genetic and dietary factors can both contribute to hyperlipidemia. Both variations gene PRKAA2 rs1124900 and ABCA1 rs2066714 are association in changes of lipid profile [7–10]. In addition to *de novo* cholesterol synthesis variation gene of PRKAA2 rs1124900 influences in elevated blood cholesterol levels. Variation gene of ABCA1 rs2066714 plays a key role in cholesterol efflux from cells during HDL maturation by elevated plasma HDL-cholesterol levels [8, 9]. Previous research on hyperlipidemic patients in Mexico found that the ABCA1 R230C genotype showed a higher response of HDL cholesterol levels to soy protein and soluble fiber ingestion [11].

The nutritional intake strategy has little detrimental consequences on preventative and adjuvant therapy. Isomaltooligosaccharide (IMO) is fermented in the colon and produce Short Chain Fatty Acid (SCFA).

SCFA has been shown to affect AMPK and ABCA, which can affect blood lipid levels [12, 13]. *In vivo* studies on rats with diabetes mellitus found that consuming IMO reduced overall cholesterol and triglyceride levels [13]. A prior study indicated that fibercreme cookies with IMO content consumption can lower CRI1 [14]. IMO have been shown to decrease have hypolipidemic and effects cardiovascular risk by decrease CRI1. However, the effect of IMO on hyperlipidemic patients with various genotype variants have not been investigated. The purpose of this study was to examine the changes in CRI1 of hyperlipidemic participants with genotype variants PRKAA2 rs1124900 and ABCA1 rs2066714 who consumed IMO cookies.

Material and methods

Study design and patients

This research is a descriptive analytic study that used 60 DNA isolates separated into two groups given different cookies: 1) IMO cookies, contain with FiberCreme (PT Lautan Natural Krimerindo) (n=30) and 2) control cookies, contain coconut milk (n=30). Table 1 shows composition of IMO cookies dan control cookies. The inclusion criteria for hyperlipidemic subjects were age 20–60 years, fasting total cholesterol levels of 190 mg/dL and/or fasting triglyceride levels of 150 mg/dL, and a willingness to sign informed consent. This study is a follow-up to the study by Prof. Dr. Dra. Sunarti, M. Kes [15] and have received ethical clearance from the Faculty of Medicine, Public Health, and Nursing Gadjah Mada University, Yogyakarta, Indonesia (KE/FK/1355/EC/2023).

Laboratory, anthropometric and clinical data collection

In the previous trial, hyperlipidemic patients were given a 4-week regimen of IMO cookies and coconut milk. Anthropometric data, a short form food frequency questionnaire (SF-FFQ), and plasma lipid measurements such as total cholesterol and HDL were taken before and after the trial. Blood lipid levels were calculated from pre-study data collected using an enzymatic colorimetric method and a Roche diagnostic kit (F.Hoffmann-La Roche Ltd., Basel, Switzerland). Peripheral blood was used for extracting genomic DNA using standard procedures (Promega WizardTM Genomic DNA Purification Kits).

Measurement data

CRI1 was measured by calculating the ratio of plasma total cholesterol to HDL cholesterol.

Genotype analysis

DNA isolates were stored in a freezer at -20˚C. DNA isolates were measured for quality and stringency using NanoDrop. Primers were ordered from Genetika Science (PT. Genetika Science Indonesia, Jakarta, Indonesia). Genotype analysis for PRKAA2 rs1124900 and ABCA1 rs2066714 used Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) with an Applied Biosystem Veriti 96 PCR Thermalcycler. The total PCR reaction volume of both genotype variations was 25 µL containing 12.5 µL Powerpol 2x PCR with dye Master Mix, 9.5 µL nuclease free water, 1 µL forward primer, 1 µL reverse primer, and 2 µL sample DNA isolate. PCR conditions were as following: Pre-denaturation 98˚C for 45 seconds, followed by 35 cycles of denaturation 98˚C for 10 seconds, annealing 57˚C for 30 seconds, elongation 72˚C for 30 seconds then final elongation 72˚C for 5 minutes. The PRKAA2 rs1124900 genotypes was amplified using primers 5'-TGGAGGATTTGAGGCTGAGGA-3' (forward) and 5'-GCCTACCCAGCATTTCTTCAG-3' (reverse) [7]. 10 L of DNA fragment was cut using AfiIII restriction enzyme (New England Biolabs Inc.), incubated for 16 hours at 37˚C, electrophoresed with 3% agarose, and visualized using geldoc. TT genotypes were 196 bp and 136 bp; TG genotypes were 196 bp, 136 bp, and 332 bp; and GG genotypes were 332 bp. The ABCA1 rs2066714 genotypes was amplified using primers 5'-GAGAAGAGCCACCCTGG TTCCAACCAGAAGAGGAT-3' (forward) and 5'-AAGGC AGGAGACATCGCTT-3' (reverse) [16]. 10 L of DNA was cut using EcoRV restriction enzyme (New England Biolabs Inc.), incubated for 16 hours at 37˚C, electrophoresed with 3% agarose, and visualized using geldoc. Genotype AA had 96 bp and 35 bp; AG had 129 bp, 96 bp, and 35 bp; and GG had 129 bp.

Statistical analysis

SPSS version 26 for Macbook (IBM Corp, USA) was used for statistical analysis. The Shapiro-Wilk were used for test data normality. The Mann-Whitney test and the independent t-test were used for analyzing characteristic data. The Wilcoxon test was used to examine groups that were not regularly distributed. The paired t-test was used to analyze groups that were

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Table 1: Composition of IMO and control cookies.

Components	IMO cookies	Control cookies
Carbohydrate	71.89	69.82
Fat	11.45	11.98
Protein	5.04	4.83
Water	4.73	7.31
Fiber	5.78	4.09
Resistant starch	2.21	1.74

regularly distributed. The one-way ANOVA was used to analyze data with more than two groups. The General Linear Method was used to examine changes in CRI1 as a result of the interaction between genotype variation and cookie intervention. A P value of less than 0.05 was considered as significant.

Results

In this study, 60 DNA isolates were separated into two groups: the IMO (n=30) group and the control group (n=30). To ensure that the baseline characteristics of research participants were similar, we statistically compared the characteristics of the two groups. Table 2 shows that the subjects' baseline characteristics did not differ significantly.

Figure 1 depicts the changes in mean CRI1 for both groups, as well as the changes in mean CRI1 before and after the intervention of IMO cookies and control cookies. Then, changes in CRI1 was analyzed and compared between the groups given IMO cookies and control cookies. The mean CRI1 in the IMO group decreased considerably after intervention ($p<0.05$). Interestingly, the mean CRI1 of the coconut milk group increased after the intervention, however it was not statistically significant ($p>0.05$).

The subjects PRKAA2 rs1124900 genotypes in all group were TT (n=34), TG (n=22), and GG (n=4). The electrophoretic visualization of PRKAA1 rs1124900 PCR

Table 2: Baseline characteristics of hyperlipidemic subjects.

Characteristics	Types of cookies		p
	IMO (n=30)	Control (n=30)	
Gender (L/P)	8/22	14/16	0.108 ^
BMI (kg/m²)	27.93±4.15 *	26.37±4.19 *	0.152 #
Total cholesterol level (mg/dl)	221.20±37.00	209.71±38.30 *	0.455 $
HDL level (mg/dl)	50.32±13.29 *	47.58±14.48 *	0.448 #
CRI 1	4.71±1.52	4.72±1.42 *	0.918 $
Nutrient intake			
Total energy (kcal)	2152.21±965.82	2000.23±720.89 *	0.660 $
Carbohydrate (g)	75.05±35.26 *	72.19±34.53	0.565 $
Fat (g)	115.11±57.86	102.56±41.44 *	0.589 $
Protein (g)	228.99±120.21	224.33±94.08	0.960 $
PUFA (g)	21.25±11.61	22.80±11.70	0.685 $
Dietary fibre (g)	29.73±22.47	27.74±16.87	0.987 $
Cholesterol (mg)	367.55±251.91	260.21±132.21 *	0.094 $

Note: ^ – chi square; * – normal data distribution ($p>0.05$); # – t-test; $ – Mann Whitney.

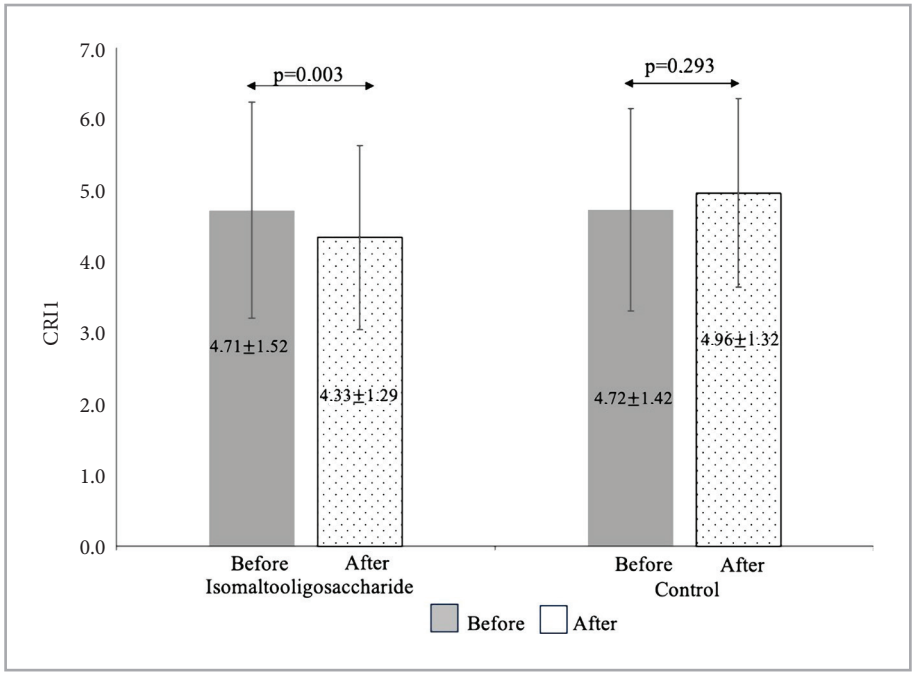

Figure 1: Intake of IMO cookies significantly reduced CRI1. CRI1 was calculated before and after supplementation of IMO and control cookies. All graphs present mean as a histogram with error bars representing starndart deviation. Significant difference if p value <0.05. IMO group; n=30, control group; n=30. Normality test using Shapiro-Wilk method, comparasion before and after suplementation in IMO group using wilcoxon test and control group using t dependent test.

products before and after enzyme cutting is shown in Figure 2. The ABCA1 rs2066714 genotype distribution in the study individuals was AG (n=31) and GG (n=29). The electrophoretic visualization of ABCA1 rs2066714 PCR products before and after enzyme cutting is shown in Figure 3.

Changes in CRI1 were observed in each group based on the difference between CRI1 before and after the intervention (ΔCRI1). Figure 4 shows the difference in response to cookie consumption of the PRKAA2 rs1124900 genotype. The PRKAA2 rs1124900 genotype (TT, and TG) had a significant effect on reduction CRI 1 in the IMO group, with p <0.05. In the control group, there was no significant influence on the difference in CRI between PRKAA2 rs1124900 genotypes.

Figure 5 shows the difference in CRI1 in genotype variation ABCA1 rs2066714 who consumed cookies there was no significant difference in ΔCRI1 score between the ABCA1 rs2066714 genotye variation given IMO cookies or control cookies (p>0.05). The interaction of

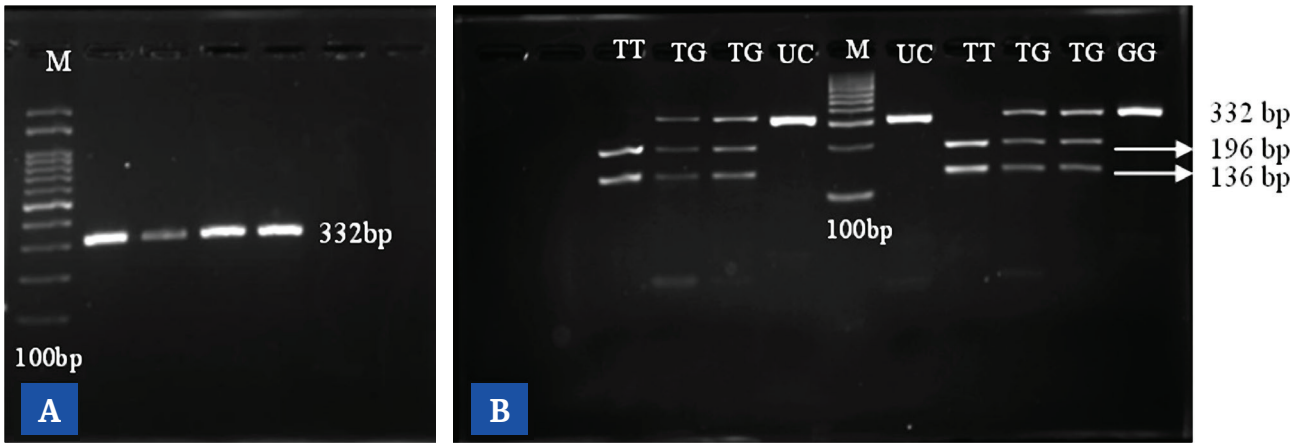

Figure 2: Electrophoresis results of PCR products and PCR product cut of PRKAA2 rs1124900. Visualization using geldoc. (A) PCR product before being cut by restriction enzyme measuring 332 bp. (B) PCR product after being cut by AfiIII restriction enzyme; TT (wild type) 196 bp and 136 bp; TG (heterozygote mutant) 332 bp, 196 bp and 136 bp; GG (homozygote mutant) 332 bp; M, DNA ladder size 100 bp; UC, uncut as control.

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ABCA1 rs2066714 genotype variation with the second intervention of cookies also had no significant effect on CRI1 ($p>0.05$).

Discussion

This study used DNA isolates of hyperlipidemic subjects who were intervened by IMO and coconut milk cookies for 4 weeks. Both cookies have almost the same nutritional composition. The two cookies use different basic components, particularly the IMO component in the fibercreme of IMO cookies and coconut milk in coconut milk cookies. This study showed the interaction of PRKAA2 rs1124900 and ABCA1 rs2066714 genotype variations with cookie intervention seen from changes in CRI1 values. The criteria for hyperlipidemia in this study were fasting total cholesterol levels ≥190 mg/dL and/or fasting triglycerides ≥150 mg/dL [17].

In this study, IMO cookies significantly reduced the mean CRI1 after intervention (8.07%). These findings are consistent with prior research by Sunarti (2022), which found that fibercreme cookies containing IMO can reduce CRI1 by 10.66%. In studies where cholesterol levels are compared to obtain CRI1, fibercreme banana porridge with IMO dramatically lowered total cholesterol levels in mice subjected to the treatment [18]. Dietary administration of 20% resistant starch was shown to reduce cholesterol absorption to 14% and effectively reduce plasma total cholesterol by 30% [19]. Consumption of 38.6 mg/dL resistant starch can reduce total cholesterol and LDL, thereby reducing the risk of cardiovascular disease by 8.8–18.9% [18]. IMO raised HDL levels by 108% in hypercholesterolemic Wistar rats fed fibercreme [20].

Resistant starch, which has fiber-like properties, increases the viscosity of the chyme hereby reducing glucose and cholesterol intake and slowing gastric emptying while also increasing bile acid excretion and fermentation in the intestine causing hypolipidemic effects [21, 22]. SCFA fermented from IMO can affect lipid metabolism by increasing AMPK activity in liver and muscle through SCFA butyrate and propionate and by increasing the ratio of AMP and ATP. Another pathway, utilizes the activation of FFAR2 and FFAR3 in adipose tissue that will increase leptin which will increase AMPK activation. This AMPK activity will inhibit the activity of HMG-CoA reductase thus reducing *de novo* cholesterol synthesis [13, 23]. Furthermore, increasing AMPK activity induces the production of PCG1-, which regulates the transcriptional activity of numerous transcription factors including PPAR-α, PPAR-β, PPAR-γ, and LXR [22]. Propionate and butyrate produced by IMO fermentation can also stimulate PPAR and LXR. ABCA1 is a transcription factor that binds to direct repeat 4 (DR-4) on the ABCA1 promoter. This will boost ABCA1 transcription, hence increasing HDL levels [23–29]. Reduced total cholesterol levels and increased HDL levels lower CRI1 readings, lowering the risk of ischemic heart events caused by hyperlipidemia.

PRKAA2 rs1124900 TT & TG genotypes interaction reaction with IMO cookies had a significant effect on the difference in CRI 1 (ΔCRI1). The TT genotype had a lower CRI1 reduction than the TG and GG genotypes. Meanwhile, the reduction in CRI1 in the TT genotype was greater in participants who had coconut milk cookies. Different responses to coconut milk cookies were seen in the TG and GG genotypes, resulting in an elevation of CRI1. This demonstrates that the three

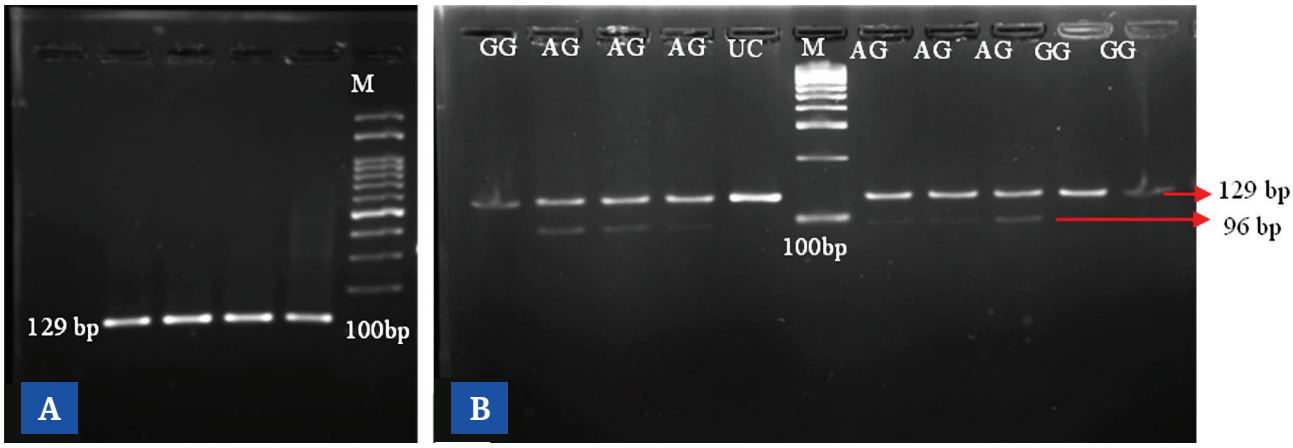

Figure 3: Electrophoresis results of PCR products and cutting of ABCA1 PCR products. Visualization using gel-doc. (A) PCR product before PCR product cutting by restriction enzyme measuring 129 bp. (B) PCR products after cutting PCR products by restriction enzymes; AG (heterozygote mutant) 129 bp, 96 bp & 35 bp; GG (homozygote mutant) 129 bp; M, DNA ladder size 100 bp; UC, uncut as control.

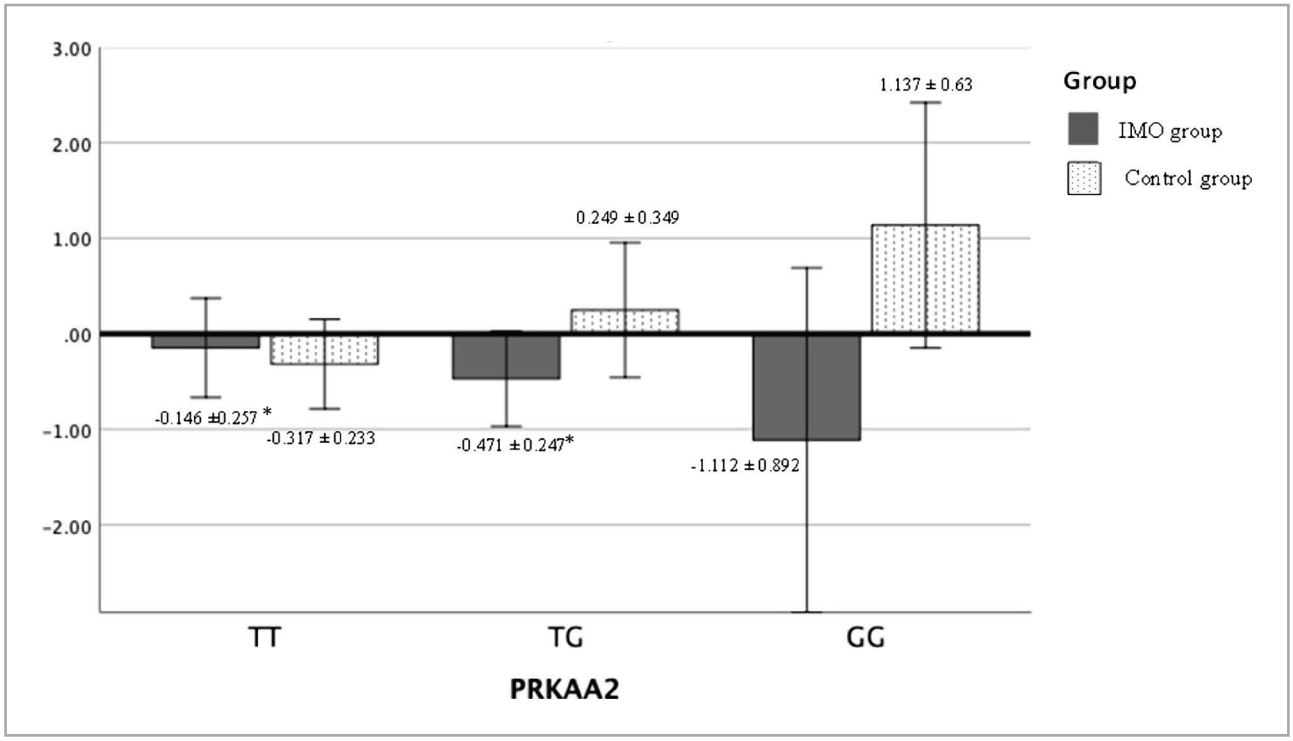

Figure 4: Effect of cookies and PRKAA2 rs1124900 genotype on CRI1. TT wild type, TG heterozygote mutant, and GG homozygote mutant. IMO group, TT; n=15, TG; n=14, GG; n=1. Control Group, TT;n=16, TG; n=7; GG; n=2. All graphs present mean as a histogram with error bars representing standart deviation. Data analysis interaction cookies and genotype by general linear model. Nutrient intake was controlled using SPSS with values of total energy=1768.50 kcal; protein=69.09 g; carbohydrate=202.38 g; fat=88.77 g; dietary fibre=21.22 g; PUFA=22.89 g; cholesterol=288.34 g. *p<0.05 in the IMO group.

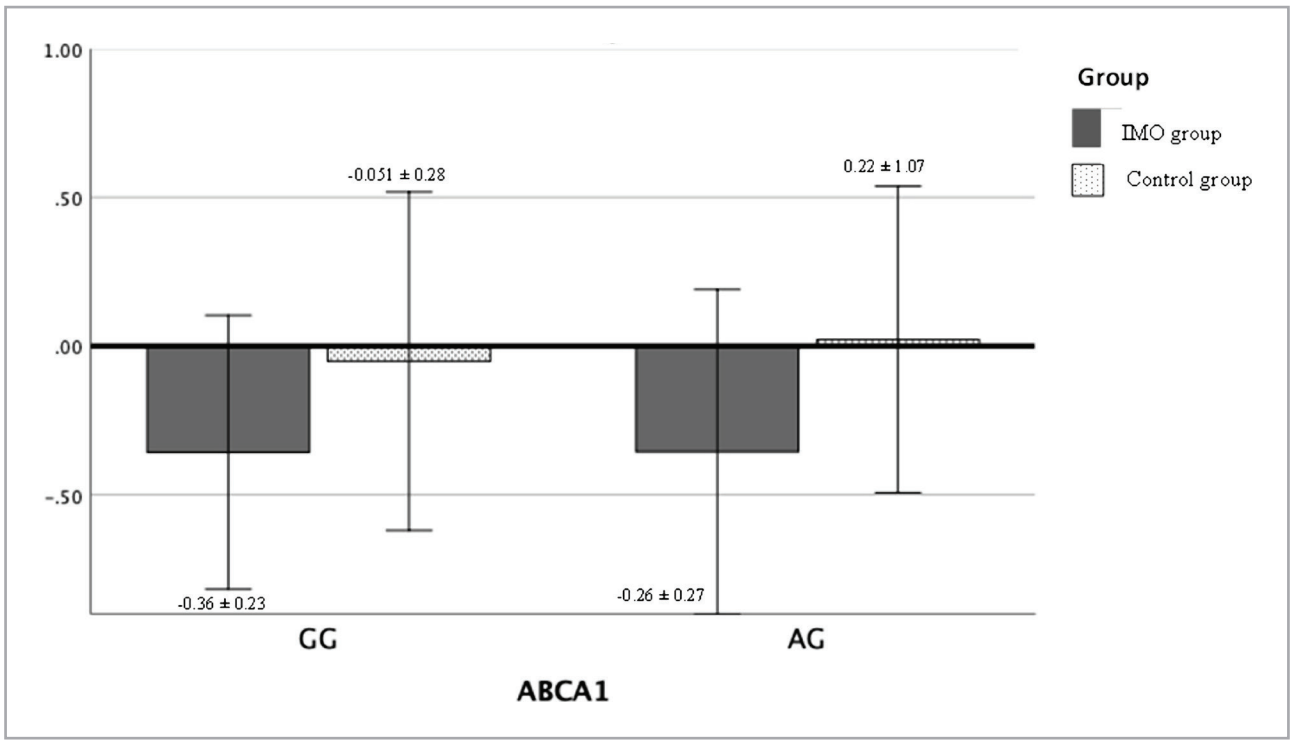

Figure 5: Effect of cookies and ABCA1 rs2066714 genotype on CRI1. AG heterozygote mutant, and GG homozygote mutant. IMO group, GG; n=13, AG; n=17. Control group, GG; n=11, AG;n=14. All graphs present mean as a histogram with error bars representing standart deviation. Data analysis interaction cookies and genotype by general linear model. Nutrient intake was controlled using SPSS with values of total energy=1768.50 kcal; protein=69.09 g; carbohydrate=202.38 g; fat=88.77 g; dietary fiber=21.22 g; PUFA=22.89 g; cholesterol=288.34 g.

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genotypes have distinct reactions to cookie consumption. Previous research has linked the minor alleles of PRKAA2 rs1124900, TG and GG, to have elevated levels of total and LDL cholesterol [7]. However, disparities in genotype reactions to ingested cookies were discovered in the present study. Consuming IMO cookies can lessen the risk of ischemic heart disease in people with the TG and GG genotypes. There has been no prior research on the interaction of the PRKAA2 rs1124900 genotype variant with IMO cookies. However, Vesnina *et al*. described the effects of genetic differences, including genetic variations in lipid metabolism, that can alter the occurrence of ischemic heart disease [29].

The interaction of cookies with genotypes between groups in the ABCA1 rs2066714 genotype did not impact CRI1 substantially. The CRI1 difference was negative in the IMO group, showing a decrease in CRI1 following the intervention. The AG genotype increased CRI1 higher than the GG genotype in the IMO group. This is consistent with Fawzy's findings which showed that the GG genotype had a more elevated HDL level than the AG genotype [30, 31]. The individuals with the AG genotype in the coconut milk group had a positive ΔCRI1, suggesting that CRI1 improved following the coconut milk cookie intervention. ΔCRI1 in the GG genotype group diminished following the coconut milk intervention. It is safe to say that the G allele is a protective allele. Due to the two cookies not directly interacting with the ABCA1 gene, the interaction of the ABCA1 rs2066714 genotype with cookies had no significant influence on ΔCRI1. Propionate and butyrate, by products of IMO fermentation by gut bacteria, interact more with PPAR, which becomes a transcription factor of the ABCA1 gene and a transcription factor of LXR that binds to the DR-4 element sequence, increasing ABCA1 expression [31, 32]. The outcomes of this study, on the other hand, can demonstrate the effect of the AG and GG genotypes reactions to diverse interventions. CRI1 is decreased by both genotypes in the IMO group, however the AG and GG genotypes in the coconut milk group responded differently.

Conclusion

The study's limitation is that no sequencing was performed to confirm the genotypic variation of both genes; consequently, the AA genotype in ABCA1 rs2066714 was not discovered, which can be overcome by increasing the sample size. This study found that IMO cookies can reduce CRI1 by 8.06% and that the interaction of PRKAA2 rs1124900 TG and GG genotypes with IMO cookies can reduce the risk of ischemic heart disease. Future study should investigate more complex genetic mutation could alter the outcome this intervention. Further inside is required true more rigorous studies with a wider sample size.

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Conflict of interest

The authors declare no conflict of interest.

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