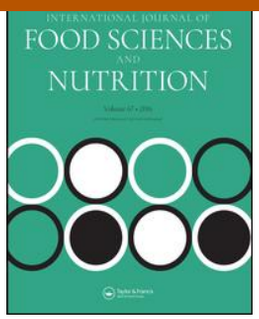

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RESEARCH ARTICLE

Nutritional factors influencing plasma adiponectin levels: results from a randomised controlled study with whole-grain cereals

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ABSTRACT

Data from intervention studies about the effects of a high intake of whole-grain cereals on adiponectin expression are still inconclusive. We evaluated the effects of whole-grain or refined cereals on fasting and postprandial serum adiponectin in people at high cardiovascular risk. According to a randomised controlled parallel group design, participants with metabolic syndrome were assigned to an isoenergetic diet based on either whole-grain cereal (WGC) or refined cereal (RC) products for 12-weeks. Anthropometric and biochemical measures were taken. Compared to baseline, fasting and postprandial serum adiponectin levels increased after both RC and WGC. In the WGC and RC groups combined, adiponectin concentrations significantly increased after 12-week intervention, and are directly associated with plasma SCFAs and acetate. Only increasing whole-grain cereals may not influence adiponectin levels, which could be modified by a fibre rich, low-fat, low-glycemic index diet, possibly through changes in gut microbiota, as suggested by the relation with SCFAs.
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Adiponectin; whole-grain cereals; dietary fibre; postprandial metabolism; metabolic syndrome; short-chain fatty acids

Introduction

Adiponectin is an adipokine abundantly produced and secreted by adipose tissue (Nigro et al. 2014; van Andel et al. 2018). It circulates as oligomers of low-, medium- and high-molecular weight complexes, the latter being the most abundant and active form (van Andel et al. 2018). Binding to its receptors -AdipoR1, AdipoR2, and T-cadherin- adiponectin plays many functions in various organs and tissues (van Andel et al. 2018). Adiponectin plays a key role in mediating the inflammatory reaction in acute cardiac and kidney disease (Fantuzzi 2013). Adiponectin is inversely associated with BMI, metabolic syndrome, insulin resistance, and type 2 diabetes (Hara et al. 2006; Basu et al. 2007; Herder et al. 2014; Nigro et al. 2014). Moreover, adiponectin inversely associates with LDL cholesterol, triglycerides, apolipoprotein B, and positively with HDL cholesterol (Miyazaki et al. 2014).

Adiponectin levels are modified by healthy dietary patterns such as the Mediterranean diet or a DASH-style diet (AlEssa et al. 2017; Nilsson et al. 2019). However, the specific dietary factors directly influencing adiponectin regulation as well as the possible mechanisms through which they may exert their effects are still undefined. A high intake of whole-grain cereals has been associated with higher plasma adiponectin levels in cross-sectional, observational studies (Qi et al. 2005; Yannakoulia et al. 2008a; AlEssa et al. 2016). However, the results of intervention studies with whole-grains were inconsistent. In a randomised controlled study in individuals with metabolic syndrome, we observed that a 12-week intervention with a whole-grain cereal-based diet reduced postprandial insulin and triglycerides responses compared to refined cereals, while no significant effects were observed on fasting parameters (Giacco et al. 2013, 2014). Moreover, plasma and adipose tissue adiponectin levels may be modified in the postprandial state, differently according to the individual metabolic status (Annuzzi et al. 2010).

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Against this background, we evaluated, in this ancillary study on the same cohorts as the previous study (Giacco et al. 2014), the effects of whole-grain or refined cereals on serum adiponectin levels in people at high cardiovascular risk in the fasting and postprandial conditions. We also evaluated the relationships between the changes in serum adiponectin and the changes in different nutritional factors during the dietary intervention.

Materials and methods

Participants and study design

Sixty-one overweight/obese individuals of both genders (23 men and 31 women), age between 40–65 years, with metabolic syndrome, participated in the dietary intervention. Details on the study design have been previously published (Giacco et al. 2013). Briefly, according to a randomised, controlled, parallel group design, after a run-in period of 4 weeks, during which subjects were stabilised on their own diet, the participants were assigned to an isoenergetic diet based on either whole-grain cereal (WGC group) or refined cereal (RC group) products for 12 weeks. They were encouraged not to change their habitual meat, dairy products, eggs, fish, fruit, vegetable and fat intake, during the whole study, being controlled by a 7-day food record filled in every month. Alcohol consumption was not allowed during the whole study duration. The only difference between the WGC and the RC groups was the inclusion of a fixed amount of whole-grain or refined cereal products as the main carbohydrate source. Therefore, the two diets were designed to have the same energy intake and nutrient composition (≈1800 kcal, 18% protein, 30% fat, 52% carbohydrates), only differing for the cereal fibre intake. The composition of the diet followed by the participants in both groups at the baseline and after the interventions are reported in Table 1.

At baseline and at the end of the dietary intervention, participants underwent clinical investigations including measurements of body weight, waist circumference and blood pressure; after an overnight fast, blood samples were taken before and 3 h over a test-meal. The two test-meals were prepared utilising standardised amounts of refined and whole-grain products to make them similar in energy and macronutrient composition (960 kcal, 18% protein, 30% fat, 52% carbohydrate) but different in fibre content, which was higher in the meal based on whole-grain wheat products (17 vs.12 g). All participants consumed the test-meal with refined cereals at baseline, while at the end of intervention the test meals resembled the composition of the two recommended diets. This paper reports data on 46 subjects for whom adiponectin measurements were available before and after intervention. The trial was approved by the Federico II University Ethics Committee and followed the Helsinki Declaration guidelines. All participants provided written informed consent. The study was registered at ClinicalTrials.gov (identifier NCT00945854).

Table 1. Energy intake and diet composition at baseline and after the 12-week dietary intervention in the two groups (Whole-grain cereals and Refined cereals) combined ($n = 46$).

	Baseline	12-week	*p* Value
Energy (kcal/day)	1767 ± 445	2041 ± 427	0.0001
Carbohydrate (%)	51 ± 5	53 ± 5	0.018
Protein (%)	17 ± 3	18 ± 6	0.220
Total fat (%)	32 ± 4	29 ± 5	0.005
SAFA (%)	10 ± 2	9 ± 2	0.061
MUFA (%)	14 ± 2	13 ± 3	0.006
PUFA (%)	4 ± 1	4 ± 1	0.211
Cholesterol (mg/day)	238 ± 93	188 ± 55	0.0001
Total fibre (g/day)	20 ± 6	31 ± 11	0.0001
Cereal fibre (g/day)	9 ± 3	21 ± 10	0.0001
Non-cereal fibre (g/day)	11 ± 5	10 ± 4	0.437
Glycemic Index (%)	64 ± 6	59 ± 13	0.007

Data are Mean ± SD.

Blood sampling and analytical methods

At baseline and at the end of intervention, blood samples were drawn from an antecubital vein after a 12-h overnight fast and over 3 h after the meal for the measurement of plasma glucose, insulin, lipids and apolipoprotein B48 (apo B48), short chain fatty acids (SCFAs), and serum adiponectin concentrations.

Plasma glucose, triglyceride and cholesterol concentrations were assayed by enzymatic colorimetric methods (ABX Diagnostics, Montpellier, France) on an ABX Pentra 400 Autoanalyzer (ABX Diagnostics, Montpellier, France). Plasma insulin was measured by sandwich enzyme-linked immunosorbent assay method (ELISA; DIAsource ImmunoAssays S.A., Nivelles, Belgium) on Triturus Analyser (Diagnostics Grifols, S.A., Barcelona, Spain). Plasma Apo B 48 was assayed by immunoturbidimetric methods (Roche Molecular Biochemicals, Mannheim, Germany). Acetate, propionate and butyrate acids plasma concentrations were measured by gas-chromatography analysis (Hewlett Packard 5890 Series II), according to Remesy and Demigne (Remesy and Demigne 1974).

Plasma alkylresorcinol concentrations were analysed by a gas chromatography mass spectrometry-single ion monitoring method, using molecular ions for quantification (Landberg et al. 2009).

Serum total adiponectin concentrations were measured by enzyme-linked immunosorbent assay method (ELISA) as previously reported (Daniele et al. 2012). Calibration curve was performed and quantified using human recombinant Adiponectin (Biovendor R&D, USA) as a standard. Each sample, diluted 1:5000, was assayed three times in duplicate. All analyses were performed blind to the dietary group assignment.

Statistical analysis

The sample size was calculated on the primary endpoint of the original trial, considering the postprandial insulin response in order to detect a 25% difference in insulin response between the two dietary groups (WGC or RC) with 0.05 significance level and 80% power (type II error Z 0.2), assuming a 15% drop-out rate (Giacco et al. 2014).

Data are expressed as mean ± standard deviation (M ± SD), unless otherwise stated. Variables not normally distributed were analysed after logarithmic transformation. To test the effects in each intervention group, 12-week concentrations were compared to the baseline concentrations by a paired sample t test. Differences between the two experimental diets in absolute changes (12-week value minus baseline value) were evaluated by repeated measures ANOVA. The associations between serum adiponectin levels and the main clinical outcomes were explored by bivariate associations using Pearson's correlation. For all analyses, the level of statistical significance was set at $p < 0.05$ (two tails). Statistical analysis was performed according to standard methods using the Statistical Package for Social Sciences software version 21.0 (SPSS, Chicago, IL, USA).

Results

Twenty-two subjects (10 men and 12 women), aged 58 ± 8 years (mean ± SD), BMI (30.8 ± 5.4) were assigned to the RC group and 24 subjects (12 men and 12 women), aged 57 ± 9 years, BMI (31.9 ± 5.8) to the WGC group.

Dietary compliance

Dietary compliance was good in both groups as reported in Supplementary Table 1. In particular, according to the experimental protocol, at the end of the intervention, total and cereal fibre intakes were significantly different between the two groups (total fibre: 40.3 ± 9.6 vs. 20.2 ± 5.4 g/day, $p < 0.001$; cereal fibre: 29.5 ± 9.3 vs. 8.7 ± 2.9 g/day, $p < 0.001$, WGC vs. RC, respectively). Moreover, compared to baseline total plasma alkylresorcinol concentrations, the best marker of whole grain cereals intake, were significantly increased at the end of the intervention in the WGC group (130 ± 96 vs 45 ± 51 nmol/L, $p < 0.05$), while decreased in the RC group (40 ± 37 vs 54 ± 50, $p < 0.05$), with a significant difference between the two groups ($p < 0.001$). In line with the dietary recommendations given to the participants, no other significant differences were observed between the two groups in relation to the energy intake and nutrient composition of the diet during the study, except for PUFA intake, likely due to higher PUFA content in whole-grain products compared with refined ones.

Anthropometric and metabolic parameters

At baseline, the clinical characteristics of the participants were similar in both groups (Table 2). Anthropometric and metabolic results were similar in women and men (data not shown). No significant

Table 2. Anthropometric and fasting metabolic parameters at baseline and at the end of dietary intervention in the Whole-grain cereals and the Refined cereals groups.

	Refined cereals ($n = 22$)			Whole-grain cereals ($n = 24$)			
	Baseline	12-week	p (within group)	Baseline	12-week	p (within group)	p (between groups)
Body weight (kg)	86.0 ± 20.2	85.5 ± 20.6	0.22	88.9 ± 17.6	88.2 ± 16.7	0.10	0.73
Waist circumference (cm)	106 ± 12	106 ± 13	0.61	108 ± 16	108 ± 15	0.52	0.98
Plasma Glucose (mg/dl)	105 ± 8	105 ± 12	0.72	103 ± 11	104 ± 12	0.60	0.53
Plasma Insulin (μU/ml)	14.4 ± 6.8	14.1 ± 8.1	0.73	15.4 ± 9.4	16.5 ± 8.6	0.34	0.34
Plasma Triglycerides (mg/dl)	151 ± 63	145 ± 61	0.64	149 ± 50	139 ± 63	0.70	0.90
Total cholesterol (mg/dl)	199 ± 36	203 ± 32	0.51	202 ± 48	202 ± 51	0.98	0.63
HDL-Cholesterol (mg/dl)	36.9 ± 6.8	38.3 ± 7.1	0.21	42.0 ± 12.4	41.5 ± 12.6	0.68	0.23
LDL-Cholesterol (mg/dl)	132 ± 33	136 ± 32	0.40	130 ± 47	132 ± 47	0.70	0.89
Apo B-48 (μg/ml)	8.20 ± 6.75	9.03 ± 7.10	0.59	7.61 ± 8.34	7.80 ± 5.16	0.83	0.72
Plasma Acetate (μmol/L)	204 ± 91	178 ± 93	0.15	179 ± 80	154 ± 133	0.23	0.97
Plasma Propionate (μmol/L)	7.58 ± 5.02	6.29 ± 4.28	0.14	5.61 ± 4.0	7.11 ± 5.05	0.16	0.05
Plasma Butyrrate (μmol/L)	5.58 ± 3.82	5.69 ± 3.84	0.87	4.37 ± 2.77	4.74 ± 2.71	0.60	0.62
Serum Adiponectin (μg/ml)	8.2 ± 1.5	9.9 ± 1.1*	0.001	7.9 ± 1.1	9.2 ± 1.7*	0.005	0.55

Data are Mean ± SD.
*$p < 0.05$ vs baseline (Paired Sample t-Test).

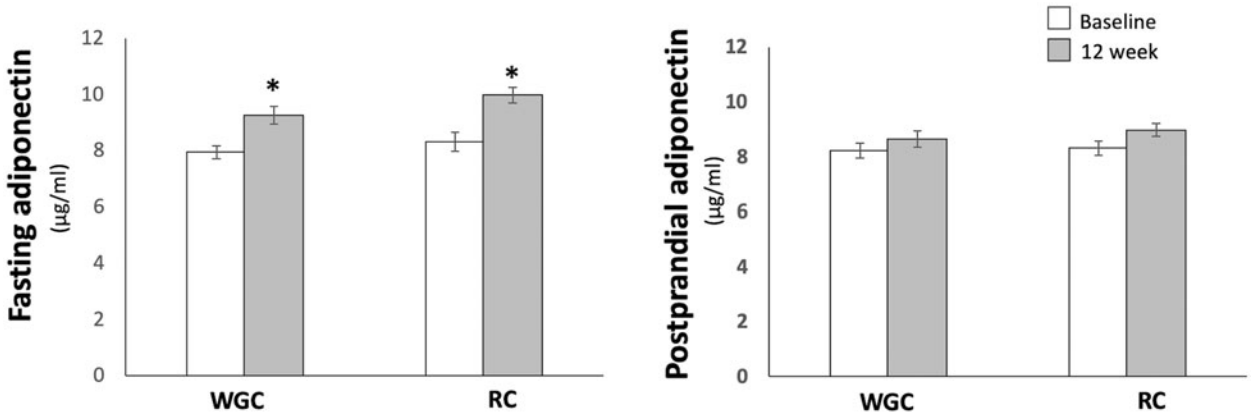

Figure 1. Fasting and postprandial (3 h after meal) serum adiponectin concentrations, at baseline (empty column) and after the 12-week intervention (gray column) in the whole grain cereals group (WGC) and refined cereals group (RC). Data are Mean ± SEM; $^{*}p < 0.05$ vs Baseline (Paired Sample T-test).

effects of the WGC and RC diets on body weight and waist circumference, and fasting plasma concentrations of glucose, cholesterol and triglycerides were observed at the end of the dietary intervention period (Table 1). As for SCFA, compared to baseline, fasting plasma acetate and butyrate concentrations did not change after intervention, whereas propionate concentrations tended to increase in the WGC group and decrease in the RC group, with a significant difference between the changes in the two groups ($p = 0.048$).

Adiponectin concentrations

At baseline, fasting serum concentrations of total adiponectin were similar in the two groups (Table 2). Compared to baseline, fasting adiponectin levels increased significantly after 12 weeks of intervention both in the WGC and RC groups, with no significant difference between the groups (Table 2, Figure 1).

Postprandial adiponectin concentrations, measured 3 h after the meal, did not change significantly after intervention compared to baseline in the WGC group ($p = 0.088$) and the RC group ($p = 0.059$) (Figure 1).

Post-intervention changes in the two groups combined

In the whole population including the WGC and the RC groups ($n = 46$), compared with baseline adiponectin concentrations significantly increased both at fasting (9.6 ± 1.6 vs. 8.1 ± 1.3 µg/ml, $p = 0.001$) and postprandially (8.8 ± 1.2 vs. 8.3 ± 1.4 µg/ml, $p = 0.010$). No significant changes of anthropometric and biochemical parameters were observed in the two groups combined. As for dietary components, compared to baseline, at the end of the intervention, energy content and carbohydrate intakes increased ($p < 0.01$); total fat, MUFA, and cholesterol intakes decreased ($p < 0.01$). Total and cereal fibre intakes significantly increased by 55% and 133%, respectively ($p < 0.05$), while glycemic index decreased (Table 1).

Correlations at baseline in the two groups combined

Fasting serum adiponectin levels were inversely associated with fasting plasma glucose ($r = -0.349$, $p = 0.017$) (Figure 2). At baseline, no other significant correlations were found between fasting adiponectin levels and metabolic parameters. Moreover, no association was found with dietary components. Postprandial serum adiponectin concentrations were inversely correlated with 3 h postprandial triglycerides ($r = -0.432$, $p = 0.003$), cholesterol ($r = -0.322$, $p = 0.029$), and apo B-48 ($r = -0.417$, $p = 0.004$) concentrations (Figure 2).

Correlations between absolute changes (12-week minus baseline)

The absolute changes (12-week *minus* baseline) in fasting serum adiponectin were directly associated with the changes in plasma acetate ($r = 0.341$, $p = 0.036$) and total SCFAs ($r = 0.346$, $p = 0.033$) (Figure 3). Adiponectin changes did not correlate with changes in body weight ($r = 0.185$, $p = 0.185$).

Among dietary components, the changes in adiponectin concentrations correlated directly with changes in energy intake ($r = 0.284$, $p = 0.05$) and inversely with changes in protein intake ($r = -0.338$, $p = 0.022$) (Figure 3).

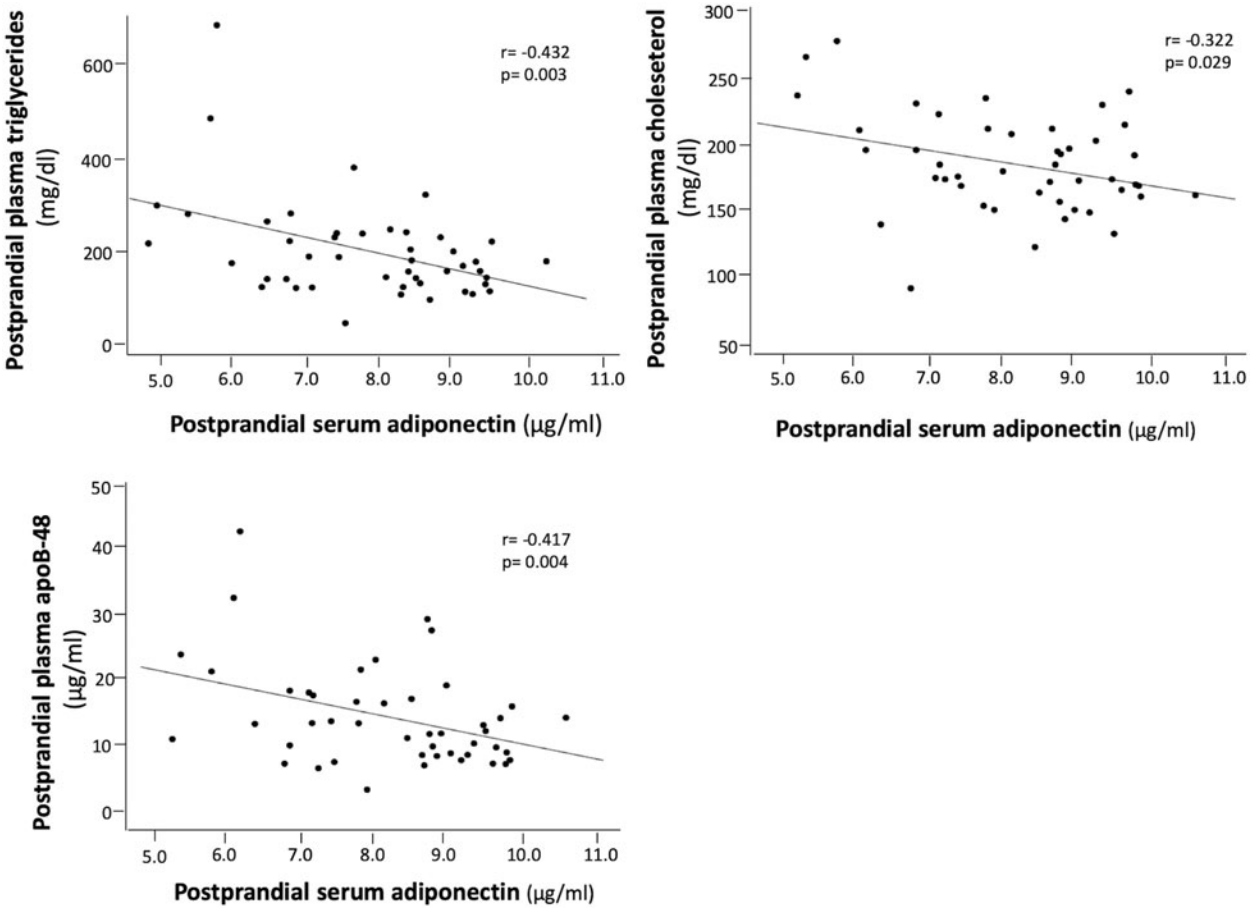

Figure 2. Simple correlations at baseline between postprandial concentrations (3 h after meal) of serum adiponectin and plasma triglycerides, cholesterol, and apo B-48 concentrations.

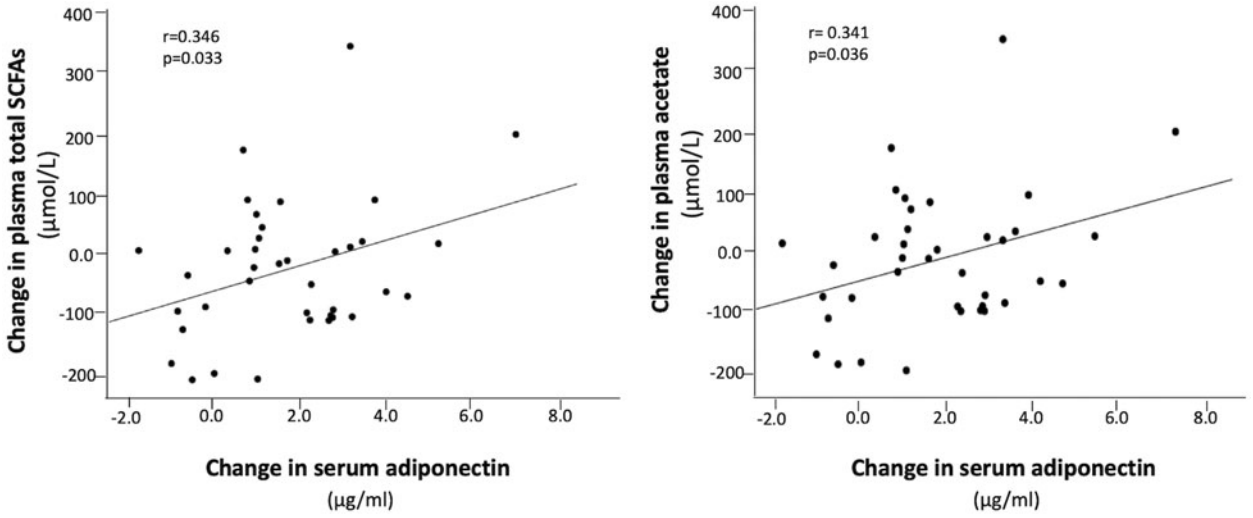

Figure 3. Simple correlations between absolute changes during the dietary intervention (12-week *minus* baseline) in fasting serum adiponectin and plasma total SCFAs and plasma acetate.

Discussion

The first finding of this study is that circulating total adiponectin levels were not significantly influenced by the type of cereals consumed, i.e. refined or whole-grain. However, adiponectin levels significantly increased in either group with high- or low- whole-grain cereals intake. This increase was associated with changes in some nutritional factors possibly acting

through modifications in gut microbiota, as suggested by the correlations between adiponectin changes and changes in plasma SCFAs and acetate.

While in contrast with some cross-sectional evidence of an inverse relation between intake of whole-grain cereals and plasma adiponectin levels (Qi et al. 2005; Yannakoulia et al. 2008b; AlEssa et al. 2016), the similar effects of whole-grain and refined cereals observed in this study are in line with the results of previous intervention trials showing no difference between whole-grain and refined grains (Harris et al. 2014; Kirwan et al. 2016). Replacing refined- with whole-grains within a weight-loss diet had only modest effects on markers of metabolic syndrome, while total adiponectin decreased with both diets with no group differences also in high-molecular-weight adiponectin (Harris et al. 2014). On the contrary, Kirwan et al. (Kirwan et al. 2016) observed that whole-grain intake preserved circulating total adiponectin concentrations compared with an ∼10% decline after refined-grain intake. The inconsistency between observational and intervention studies may indicate that other nutritional factors linked to whole-grain intake may explain the association observed in the cross-sectional analyses. Many evidences suggest that healthy dietary patterns such as the Mediterranean diet are associated with higher adiponectin levels, although it remains unclear which dietary component of these dietary patterns may play a role. In this study, because of a similar significant increase in fasting and postprandial adiponectin in both the intervention and control groups, we combined the two groups to analyse whether this increase was related to changes in other nutritional factors. In the whole cohort (Table 1), total energy intake increased significantly, because of the added cereals, with a concomitant increase in carbohydrate intake -mainly fibre from cereals – while the glycemic index of the diet decreased, and fat intake was reduced. Therefore, as a whole the participants had a healthier diet that could explain the increase in adiponectin. It is of note that, as the dietary interventions were isocaloric, all possible dietary effects on adiponectin should be ascribed to qualitative dietary changes. To this regard, no relation between changes in body weight and adiponectin was observed in line with previous evidence (Kirwan et al. 2016).

The global metabolic improvement generally associated to participating in a nutritional trial may have also contributed to increasing adiponectin levels. This is also more likely as the experimental diets were generally healthy and potentially leading to an improvement in insulin sensitivity. To this regard, as previously reported (Giacco et al. 2014), postprandial insulin sensitivity was improved by the whole-grain cereals, as it was postprandial triglycerides, which were associated with postprandial adiponectin at our baseline observation. Supporting a postprandial relationship, also plasma apo B48 and cholesterol concentrations were associated with adiponectin in the postprandial state.

Many plausible mechanisms could explain the relationship between the improvements of glucose homeostasis by whole-grain fibre (Della Pepa et al. 2018) and adiponectin levels. Interestingly, the changes in adiponectin concentrations during this study were directly associated with the changes in plasma concentrations of total SCFA and acetate. Although these fatty acids were not modified by the WGC intervention, their increase in the circulation is in line with increased dietary intakes of carbohydrate and fibre suggesting a role for the gut microbiota (Vetrani et al. 2016). This possible mechanism would deserve further investigations. Although some animal studies suggested a relation between propionate and a better blood lipid profile (Weitkunat et al. 2016), in our study propionate seemed not be involved in the adiponectin/lipid relation. Since propionate is highly metabolised in the liver, it is possible that the amount of propionate reaching the adipose tissue may be too low to influence adiponectin levels.

This study has some strengths and limitations. A strength is the randomised controlled design. A limitation is that some of the findings were obtained from a not predefined analysis of changes in dietary intakes, independent of the specific dietary intervention, i.e. WGC or RC. In conclusion, the results of this study show that only increasing whole-grain cereals may not influence circulating adiponectin level, which may be modified by associated nutritional factors, possibly through changes in gut microbiota.

Disclosure statement

No potential conflict of interest was reported by the authors.

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