Alkalinised filtered water induces changes in the gut microbiome in inflammatory bowel disease

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Submitted: 19 September 2025; **Accepted:** 4 July 2026
Online publication: 21 October 2026

Arch Med Sci 2026; 22 (5): 2755–2771
DOI: https://doi.org/10.5114/aoms/225476
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Abstract

Introduction: This study evaluated the effects of filtered, alkalinised water on inflammation and intestinal dysbiosis in individuals with inflammatory bowel disease (IBD).

Material and methods: We conducted a three-month, two-arm, randomised intervention study involving 46 patients with IBD in remission. Fifty-two volunteers were recruited and divided into two groups (n = 26): the control group consumed water from a mock device, and the test group consumed alkalinised filtered water. Forty-six (21/25) volunteers completed the study. Blood and stool samples were collected before and after the intervention. We assessed antioxidant capacity and circulating cytokine levels from plasma. Gene expression levels of inflammatory mediators were determined using mRNA from peripheral blood mononuclear cells (PBMCs). The microbial composition of faecal samples was characterised by qPCR analysis using primers targeting 16S rRNA genes.

Results: Consumption of alkalinised filtered water significantly reduced *IL1B* gene expression in PBMCs. Furthermore, subjects drinking alkalinised filtered water exhibited a consistent, albeit not statistically significant, decrease in circulating IL-1β and significantly lower levels of IL-4 than controls. Microbiome analysis revealed that the levels of the *Bacteroides fragilis* Group were significantly reduced in subjects consuming tap water but not in those consuming filtered water.

Conclusions: These changes suggest that consuming alkalinised water for three months leads to an improved inflammatory status compared with consuming tap water.

Key words: alkalized filtered water, intestinal bowel disease, microbiome, inflammation.

Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory condition of the gastrointestinal tract affecting approximately 6.8 million people worldwide. While genetic susceptibility plays a significant role, IBD primarily arises from the impact of environmental factors on the gut microbiome [1]. For instance, genetic factors explain only ~13.1% of the variance

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for CD and 8.2% for UC [2]. The increasing incidence of IBD in newly industrialised countries underscores the influence of a Western lifestyle on risk. Environmental risk factors identified through association studies include the following: urban living, long-term use of nonsteroidal anti-inflammatory drugs, oestrogen-progesterone oral administration (e.g. contraceptives and hormone replacement therapies), antibiotic use, diet regimes high in meat/low in vegetables, and processed food consumption [3]. Current models suggest that these risk factors alter the intestinal mucosa immune response to the gut microbiome in genetically susceptible individuals.

Recent advancements in understanding complex mucosa-microbiome interactions and how diet alters microbiome composition suggest that the direct impact of diet on the microbiome is a key factor in IBD development [4]. For example, active IBD is linked to major gut microbiota shifts, including reduced overall diversity, an increase in Proteobacteria (especially Gammaproteobacteria), and a decrease in Firmicutes [5]. Conversely, healthy diet regimes and probiotics have consistently demonstrated the ability to partially reverse this dysbiosis and reduce inflammation [6].

Limited epidemiologic evidence suggests that drinking water may be a relevant risk factor for IBD, but the accumulated evidence is still very limited [7]. Evaluating the health effects of tap water consumption is a complex, challenging, and even daunting task. This complexity arises from the varying chemical compositions of tap water, which are influenced by factors such as season, rainfall, soil, and treatment processes [8]. Despite these challenges, several observational studies have explored the links between drinking water, intestinal inflammation, and IBD. Specifically, the presence of iron [9] and other metals, nitrates [10], sulphites, disinfectants, and surfactants [7, 11] have all been associated with intestinal inflammation and IBD incidence. More recently, studies are also examining the contribution of microplastics in water to IBD [12].

Overall, growing health concerns regarding increasing and highly variable pollutant by-products in drinking water (such as metals, microplastics, and persistent organic compounds) have boosted the use of spring/purified bottled water and water filter systems [13]. These alternatives can significantly reduce the concentration of hazardous substances in tap water and can also positively impact the gut microbiome [14].

Water filtering systems also known as point-of-use water filters, can be grouped into four basic categories: 1) particle filters, which remove solid particles but do not alter the water chemistry; 2) reverse osmosis systems, which reduce the total concentration of ions; 3) activated charcoal filters, which are particularly effective in removing chlorine (Cl^-) and organic compounds; and 4) alternative systems, such as alkalinising water devices.

Alkalinised water has been recommended for patients with gastric acidosis [15], and in Japan, accumulated evidence has led to the approval of electrolysed alkaline-reduced water (EARW) apparatuses as medical devices. The impact of drinking water pH on the microbiome is also well established [16], prompting investigations into the potential intestinal benefits of alkalinised water consumption. However, the beneficial effects of EARW consumption remain controversial [15, 17]. Filter-based ion-exchange systems offer an alternative to electrolysis for alkalinising water, but scientific studies on their health benefits are still in their early stages. Our previous research in rodents showed that filtered alkaline water consumption improved vascular reactivity and reduced systemic inflammation [18]. We then sought to determine if this anti-inflammatory activity was linked to intestinal effects. To that end, we used lean and obese Zucker rats, a common preclinical model for obesity and diabetes research due to their insulin resistance, glucose intolerance, and metabolic syndrome [19]. We treated these rats with either tap water or alkalinised filtered water for three months. Our findings revealed that the filtered water reduced intestinal inflammation and oxidative stress markers, improved the intestinal mucosa status, and positively affected the microbiome profile in stool samples [20]. Given these promising results, we conducted a human intervention to see if alkalinised filtered water could positively impact intestinal dysbiosis and inflammation in patients with IBD. After 3 months of alkalinised water use, we observed changes indicative of an improved inflammatory profile compared with subjects who drank tap water.

Material and methods

Human subjects

This pilot, longitudinal, prospective, randomised, and parallel nutritional intervention study involved two groups. We advertised the study via social media, and interested individuals were fully informed about the study. In total, 52 volunteers signed the informed consent form, and 46 completed the study. The main inclusion criteria were to be an adult with a diagnosis of IBD, with a self-reported remission phase, who could provide informed consent. Exclusion criteria included comorbidities and confounding pharmacological treatments including recent antibiotic intake. Volunteers were asked to drink filtered water for three months, and they received filtering jars containing either active filters (Alkanatur® Drops SLU, Milladoiro-Ames, A Coruña, Spain) or

mock filters (Tap). An authorised laboratory (Oliver Rodés) analysed the water filtering system, confirming its compliance with UNE 149101:2015 standards for human consumption. This system has been shown to remove trihalomethanes and Cl^-, while adding 15 mg/l of Mg^{2+}; it has also been shown to provide water free of microorganisms, and not to release sodium (Na^+). The plastic jar was approved for food contact and was shown to be free of bisphenol A, epoxidized soybean oil, and phthalate esters [21]. The pH of tap water is not fully stable, but on average the pH in the city of Madrid is reported to be between a minimum of 6.5 and a maximum of 9.5, more commonly between 7 and 8.5. At the IIBM, where the researchers are located, we generally observe a pH between 7 and 7.5 for tap water. This information can be found at the official web page of Madrid City Local Government: https://madridsalud.es/salud-publica/control-aguas/ and of the Water provider: https://www.canaldeisabelsegunda.es/calidad-del-agua. At the IIBM the pH increases to 9-9.5 following filtration, as reported by the filter makers: https://alkanatur.com/es/.

A professional nurse collected blood and stool samples at the School of Medicine of the UAM before and after the study. Fasting blood samples were drawn from the cubital vein into BD Vacutainer tubes with EDTA (Becton Dickinson, San Jose, CA; Cat. No. 368589) early in the morning. These samples were used to isolate plasma and PBMCs using density-gradient Ficoll-Paque-PLUS separation (Cytiva, Marlborough, MA; Cat. No. 11768538). Stool samples were collected in sterile containers (Acofarma, Madrid, Spain; Cat. No. 311218), then frozen and stored at –80°C until processing. The study received approval from the Ethics Committees of the IIBM, the UAM, and the Spanish Scientific Research Council (*Consejo Superior de Investigaciones Científicas*, CSIC).

Microbiome

DNA was purified from collected stool samples using the QIAamp® Fast DNA Stool Mini Kit (Quiagen, Cat. No. 51604). Bacterial quantification was performed by qPCR using primers specific to the bacterial groups: *Bacteroides Fragilis* Group, *Blautia coccoides-Eubacterium rectale* Group, *Clostridium* cluster IV, *Bifidobacterium* spp., *Lactobacillus* spp., *Enterobacteriaceae*, *Enterococcus* spp., *Faecaibacterium praustnizii*, and *Akkermansia muciniphila* directed against 16S rRNA coding genes, as previously reported [20].

Gene expression analysis

Total mRNA was isolated from PBMCs and used as a template for cDNA preparation, which was then analysed by qPCR, as previously reported [20]. *36B4* was used as a loading control.

Cytokines

Circulating levels of IL-1β, IL-4, IL-6, TNF-α, and IL-10 in plasma were analysed by cellular cytometry using Multiplex Cytokine Assays (Pro-cartaPlex Immunoassays, ThermoFisher Scientific) at the CNB (CSIC) Flow Cytometry Unit.

Antioxidant capacity

Antioxidant capacity was determined in plasma samples using the e-BQC electrochemical analytical system (BioQuoChem, Oviedo, Spain), which measures total (QT), and fast- (Q1) and slow-acting (Q2) antioxidant capacity.

Statistical analysis

Microsoft Excel (Microsoft Corp., Redmond, WA) was used for data processing. GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA) was used for statistical analysis and graph preparation. The normality of the data was assessed using the Kolmogorov-Smirnov test. Statistical significance of differences between groups was assessed using two-tailed *t*-test, and two-way ANOVA for continuous variables. Levene's test was used for equality of variances. Fisher's exact test was used for discontinuous variables. The values were considered statistically significant when $p < 0.05$. No values were discarded; those values not included were due to failure in sample acquisition or technical problems.

Results and Discussion

To assess the effects of alkalinised filtered water in patients with IBD, we conducted a three-month intervention study. Fifty-two volunteers signed informed consent forms. We randomly assigned 26 participants to receive a mock filter unit and 26 to receive an active filter unit (Table I). Participants were asked to complete a form with epidemiological data and use their assigned unit for all drinking water over the study period. Blood and stool samples were collected prior to the initiation of the study and following the three-month intervention. Participants received no compensation. Ultimately, 46 subjects completed the study: 25 used the active filtering unit and 21 used the mock filtering unit. Therefore, only one person from the active filter group dropped out compared with five from the mock filter group.

Circulating cytokines

Following the intervention, the levels of IL-4 were significantly lower in the filtered water group

Table I. Baseline cohort characteristics

Parameter	Tap (n = 21)	SD	Filter (n = 25)	SD	P-value
Drop-out	5		1		0.19
Males	5		8		0.74
Females	16		17		
Age [year]	41.24	8.85	38.76	11.16	0.41
Weight [kg]	65.24	14.68	65.01	12.59	0.96
Body mass index (BMI)	24.02	4.38	23.14	3.58	0.47
Crohn's disease (CD)	14		14		0.76
Ulcerative colitis (UC)	5		12		

than in the tap water group, along with a trend for reduced IL-1β levels (p = 0.05). However, no significant differences were found when comparing the two intervention groups (Figure 1).

Overall, neither group experienced an increase in any of the tested cytokines over time. While the observed reductions were not statistically significant, the filtered water group generally showed slightly greater reductions for all cytokines apart from IL-10 (Figure 2). This suggests that drinking alkalinised filtered water may have a mild immunomodulatory effect.

Analysis of cytokine gene expression

The analysis of circulating cytokines was complemented with a gene expression analysis in PBMCs: *IL1B* (encoding IL-1β), *IL*4, *IL6*, *IL-10*, *TGFB1* (encoding TGFβ), *TNF* (encoding TNFα), and *IFNG* (encoding IFNγ). Following the intervention, the mRNA levels of *IL1B* were significantly higher in the tap water group, while the filtered water group exhibited no such response. This led to significant differences in *IL1B* expression between the groups after the intervention. No other significant changes were identified in the remaining genes tested, either between groups or as a result of the intervention (Figure 3).

Overall, in the tap water group gene expression levels did not change with the intervention, while in the filtered water group, gene expression levels on average decreased or did not change. Nevertheless, only the differences in *IL1B* expression reached statistical significance (Figures 3, 4).

Antioxidant capacity

We next evaluated the impact of the intervention on plasma antioxidant capacity. Accordingly, fast (Q1), slow (Q2), and total (QT) antioxidant capacities were measured using an e-BQC electrochemical reader. No significant differences were observed either within or between the groups (Figures 5, 6), suggesting that the water source did not affect the plasma antioxidant capacity of the volunteers.

Overall, both intervention groups showed a non-significant trend toward reduced antioxidant capacity. Notably, the inter-individual variability in antioxidant capacity was non-significantly more reduced in the tap water group than in the filtered water group. A reduced antioxidant capacity might relate to a decreased inflammatory state, an induced compensatory antioxidant response, or a diminished systemic capacity to manage pro-oxidants. In the present context, tap water appeared to be more pro-inflammatory, while filtered water seemed more anti-inflammatory. The subtle changes observed could point to a better redox balance in individuals who drank filtered water. However, the lack of statistical significance limits the robustness of the findings, probably due to the small sample size.

Intestinal microbiome

Finally, we evaluated the impact of the intervention on the intestinal microbial composition. To do this, total DNA was isolated from stool samples collected before and after the intervention, which was analysed by qPCR. We assessed changes in nine bacterial groups previously linked to metabolic status or diet [22–30]: Bacteroides fragilis Group, Blautia coccoides-Eubacterium rectale Group, Clostridium cluster IV, Bifidobacterium spp., Lactobacillus spp., Enterobacteriaceae, Enterococcus spp., Faecaibacterium praustnizii, and Akkermansia muciniphila. In samples prior to intervention (t = 0) we found a significant difference among the groups. The levels of Bifidobacterium spp. were significantly lower in the filtered water group than in the tap water group. This unpredictable bias, despite randomised device distribution, is notable because reduced Bifidobacterium spp. has been found in patients with bowel disease and is associated with metabolic alterations such as obesity [31]. In response to the intervention, we found a significant reduction in the Bacteroides fragilis Group in the tap water group, while this effect was not observed in the filtered water group. However, no statistically significant differ-

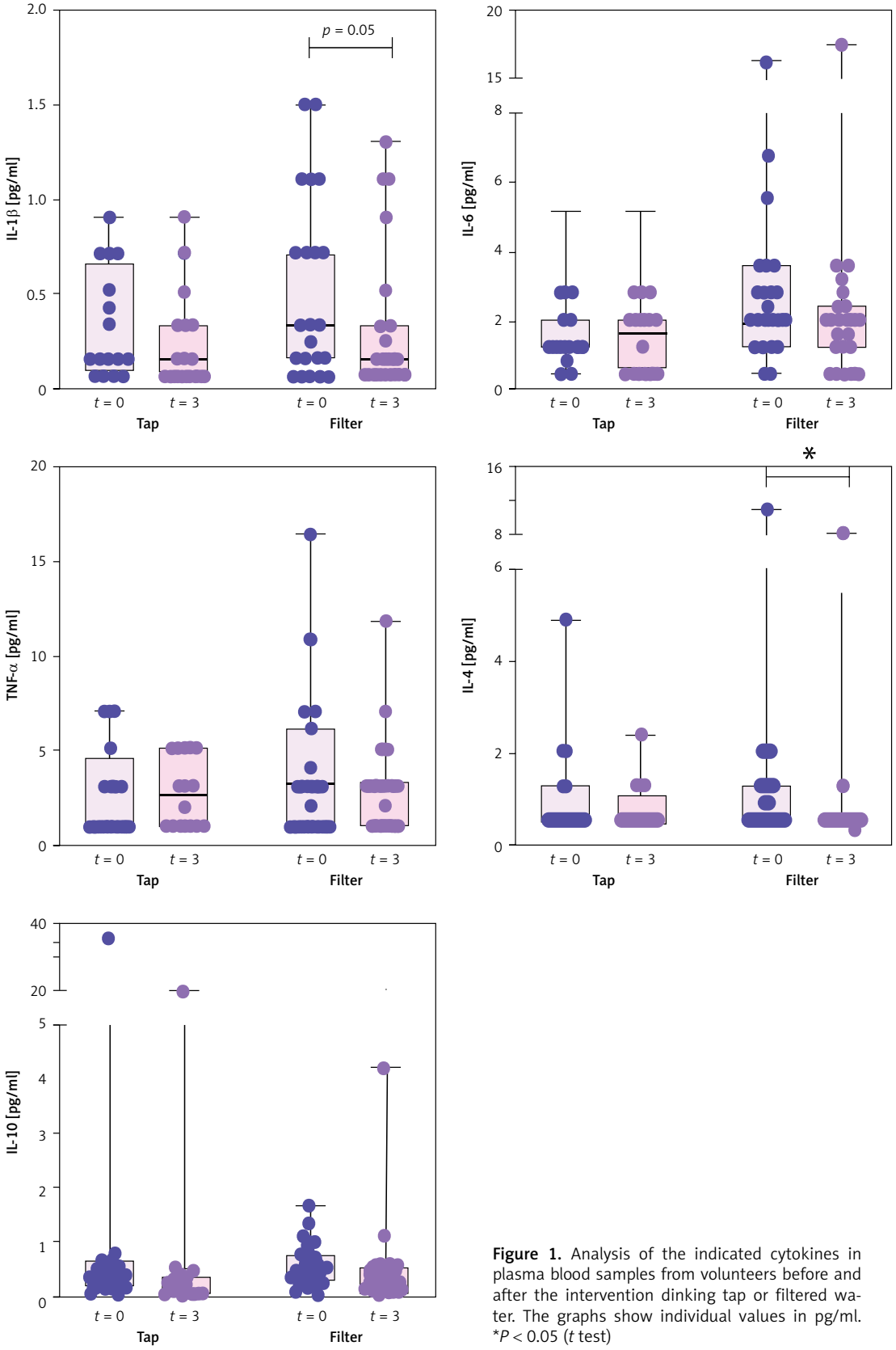


Figure 1. Analysis of the indicated cytokines in plasma blood samples from volunteers before and after the intervention dinking tap or filtered water. The graphs show individual values in pg/ml. *$P < 0.05$ (t test)

ences were found between both groups (Figure 7). The Bacteroides fragilis Group has been extensively studied, which includes common anaerobe members of the human microbiota and has been shown to provide several immunomodulatory benefits to healthy hosts [32]. Its role in IBD remains controversial. Some enterotoxic strains are elevated in IBD and are associated with the active phase of the disease [33]. Conversely, the Bacteroides fragilis Group has also been shown to alleviate the disease when used as a probiotic, because of its anti-inflammatory effects associated with IL-10 induction [34]. Similarly, in other diseases such as obesity, accumulated data suggest that these bacteria can behave differently depending on the context, playing both pro- and anti-inflammatory roles [35]. A relevant study that shed some light on this context-dependent behaviour of Bacteroides fragilis Group showed that these bacteria regulate enterotoxin gene expression by altering the orientation of the promoter of the enterotoxin gene. This modification is increased

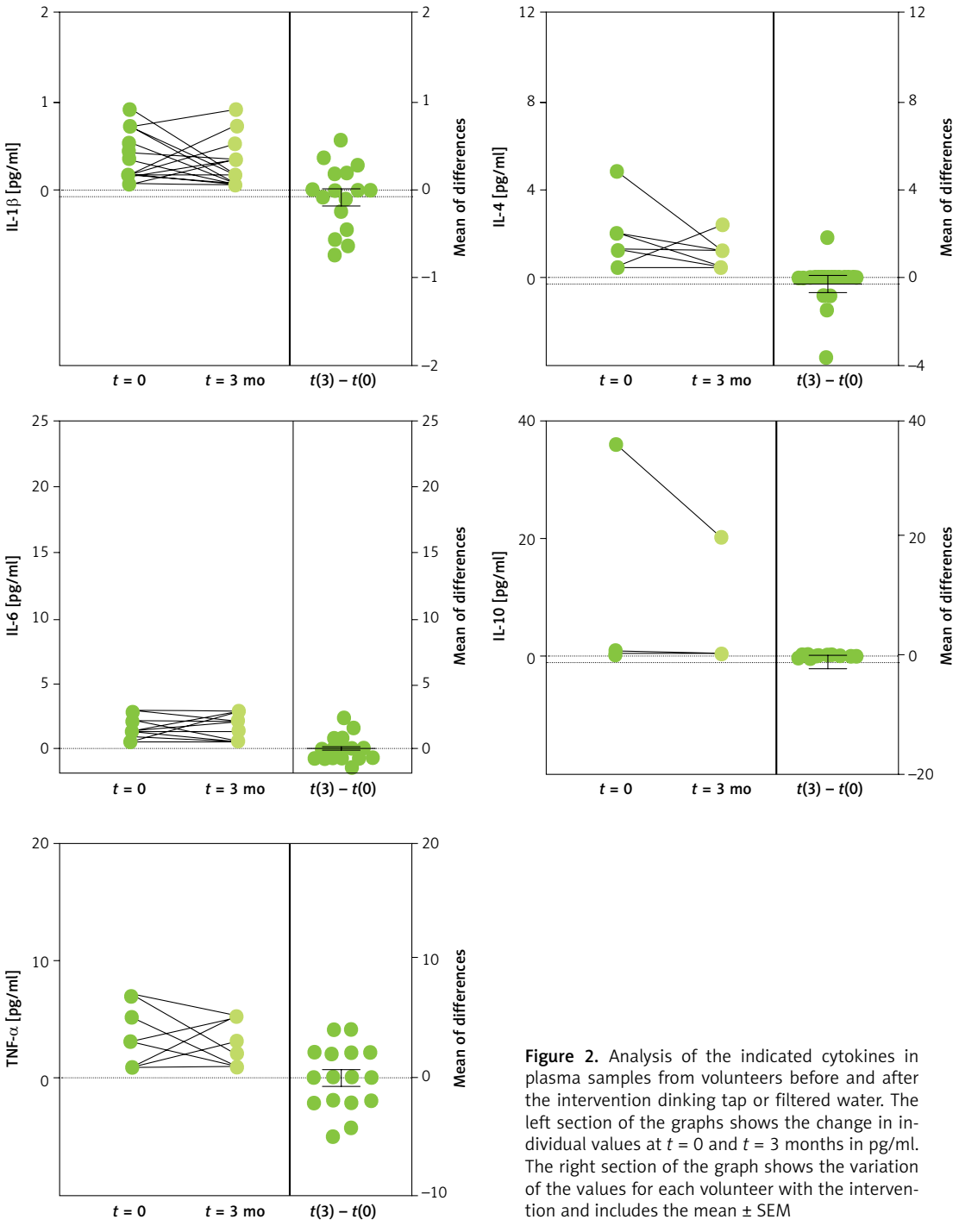


Figure 2. Analysis of the indicated cytokines in plasma samples from volunteers before and after the intervention dinking tap or filtered water. The left section of the graphs shows the change in individual values at $t = 0$ and $t = 3$ months in pg/ml. The right section of the graph shows the variation of the values for each volunteer with the intervention and includes the mean ± SEM

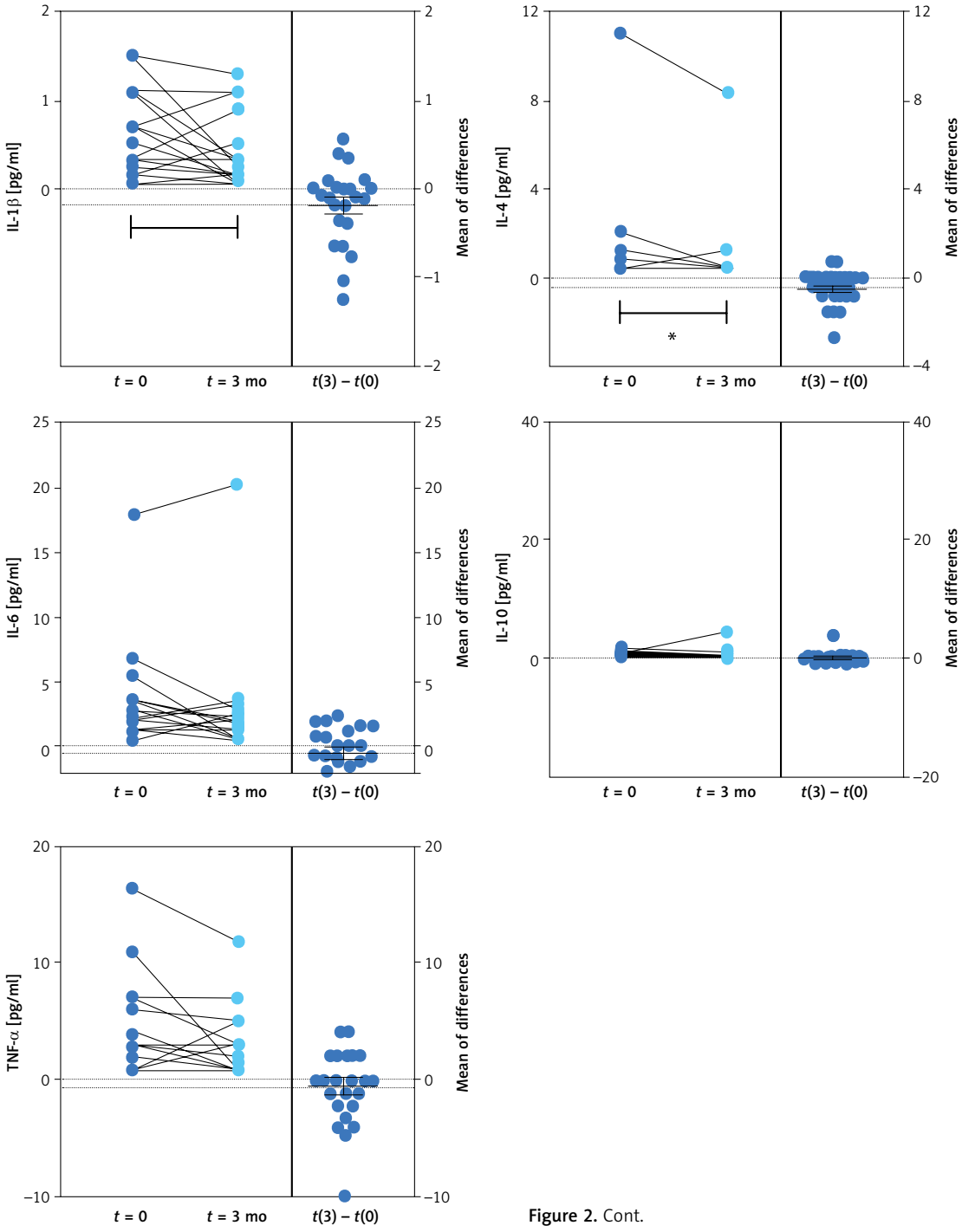


Figure 2. Cont.

in IBD and linked to its pro-inflammatory role, suggesting that such pathological promoter modification could result in a pro-inflammatory phenotype [36].

The rising prevalence of IBD has intensified the search for risk factors, and current evidence suggests that diet can contribute to disease development. Moreover, diet-associated dysbiosis is a significant component of IBD. Water, a vital dietary component, has also been identified as a risk factor for IBD.

Our prior preclinical studies in mice and rats revealed that consuming filtered water from an alkalinising device for three months reduced systemic and intestinal inflammation and improved intestinal dysbiosis compared with tap water. These findings, based on targeted microbiome analysis of faeces [20], led us to investigate similar effects in humans with IBD. The results indicated significant or near-significant trends suggesting improved inflammatory status in individuals using the alkalinising filter device. Notably, these chang-

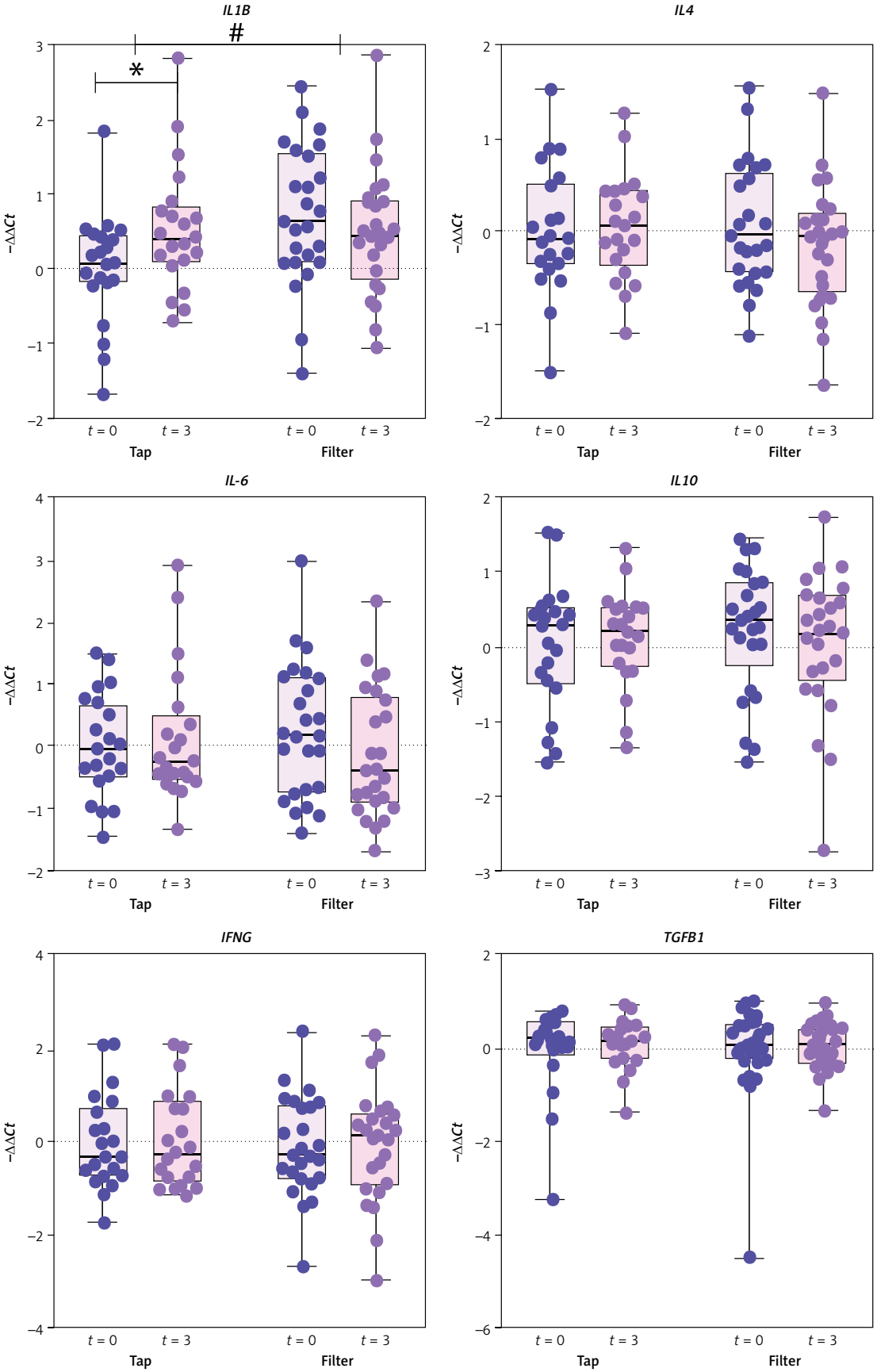
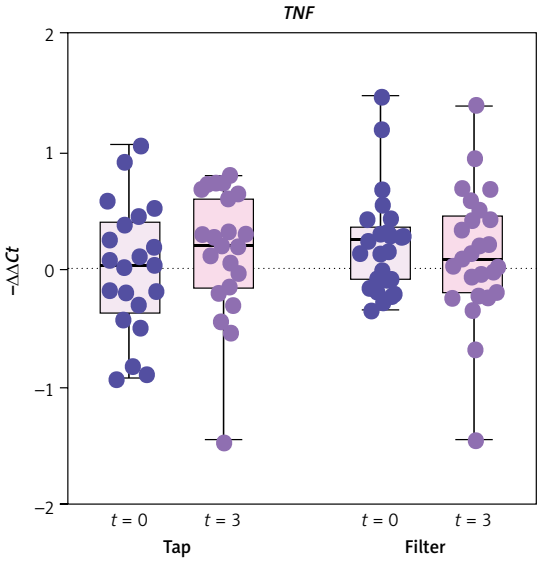


Figure 3. qRT-PCR gene expression analysis of the indicated cytokine-coding genes in PBMCs. The graphs show –ΔΔCt individual values, *36B4* was used as a loading control, and data were normalised to the mean of the tap water group prior to the intervention. *$p < 0.05$ (*t* test). #$p < 0.05$ (two-way ANOVA)



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es were consistent with our preclinical observations. Specifically, after 3 months, we observed an almost significant (p = 0.05) reduction in circulating IL-1β levels in subjects who consumed filtered water. Further supporting these findings, gene expression analysis in PBMCs showed that *IL1B* expression increased in tap water consumers. These results align with our previous findings demonstrating that filtered water consumption reduced circulating IL-1β levels in lean Zucker rats and in SHR rats after a 3-month intervention [18, 20].

These findings are particularly relevant given the extensive research supporting IL-1β as a crucial mediator of inflammation and tissue damage in IBD. Notably, intestinal dysbiosis has been shown to stimulate IL-1β release, thereby promoting inflammation [37, 38].

Since inflammation is commonly associated with oxidative stress, we evaluated changes in plasma oxidative capacity. However, no significant differences were found between the groups, probably due to the small sample size.

We conducted a targeted analysis of bacterial content in stool samples. The only significant difference linked to the intervention was a reduction in the *Bacteroides fragilis* Group in the group that consumed tap water; this effect was not seen in the group who consumed filtered water. Interestingly, our previous study with lean Zucker rats also showed that tap water consumption reduced the abundance of the *Bacteroides fragilis* Group while filtered water had the opposite effect [20]. This consistency suggests the outcome is likely functionally significant. Interpreting these findings requires considering the inflammatory status. The *Bacteroides fragilis* Group typically has an anti-inflammatory role. However, during the active phase of IBD, these bacteria can activate an enterotoxin known to negatively impact disease progression. Given the relatively high levels of IL-1β observed in the tap water group (in both rats and humans), it is plausible that the reduction of the *Bacteroides fragilis* Group in tap water consumers is linked to their increased inflammation.

Overall, these data support the hypothesis that consuming alkalinised filtered water may improve the inflammatory state in patients with IBD and potentially reduce dysbiosis, and they may also be indicative of the relevance of redox balance to control intestinal inflammation, an idea in line with data suggesting that intake of certain highly reactive xenobiotics that can be found in tap water, such as chlorinated and fluoridated molecules, is pro-inflammatory [1].

However, the study has important limitations. In particular, the small and gender unbalanced sample size, the limited number biomarkers evaluated, and the lack of a standardised clinical follow-up evidence that further research with a more extended follow-up period is needed to confirm the significance of these findings.

Acknowledgments

Technical support was provided by Raquel García. Editorial support was provided by Dr. Kenneth McCreath. Our special thanks to ACCU ESPAÑA and ACCU Madrid for supporting and guiding the preparation of the study, the social media advertisements and their distribution, as well for providing the necessary framework for the registration of volunteers and collection of demographic data.

Funding

This research was funded by Alkanatur under the supporting technological contract ALK-Crohn

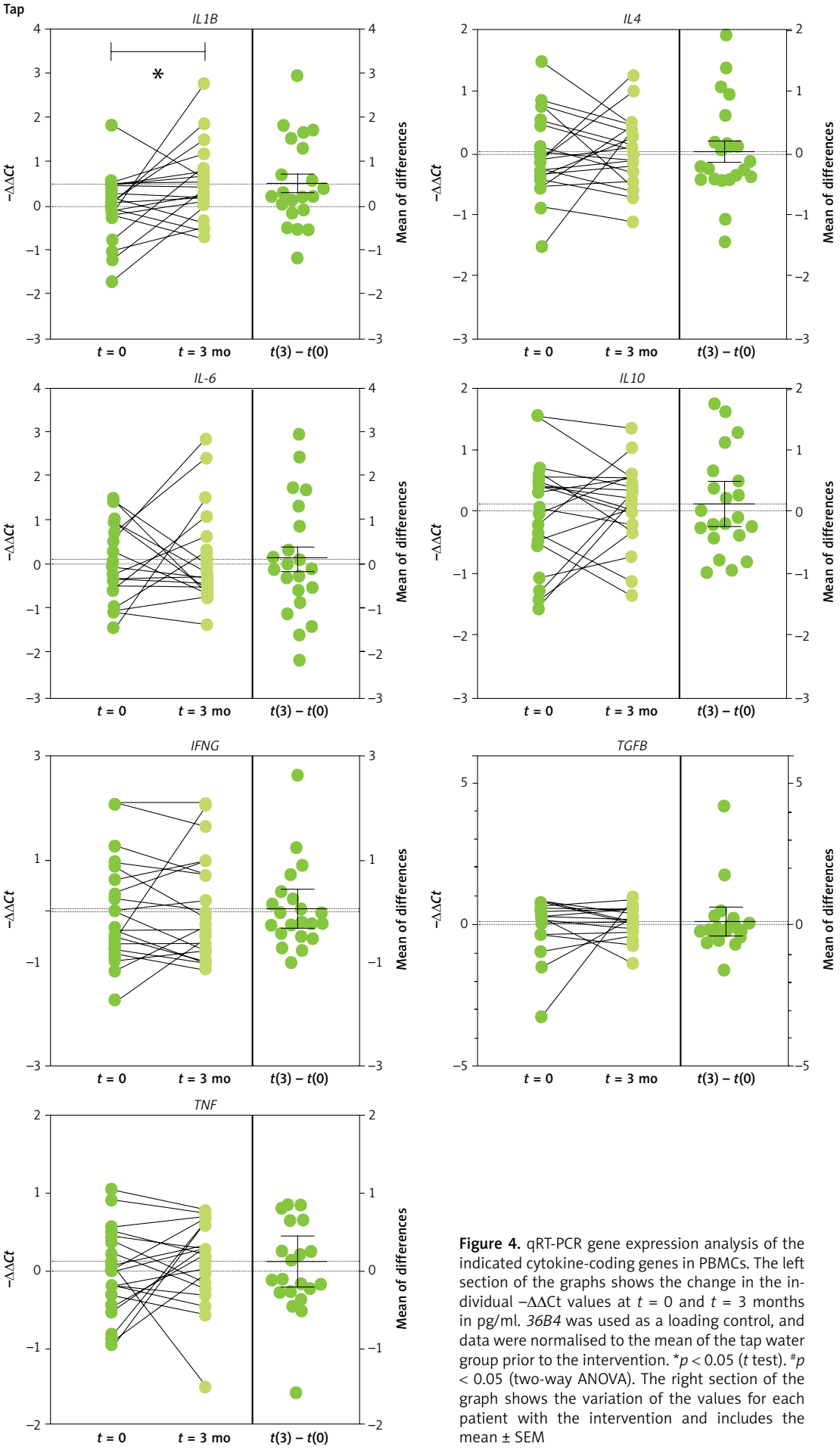
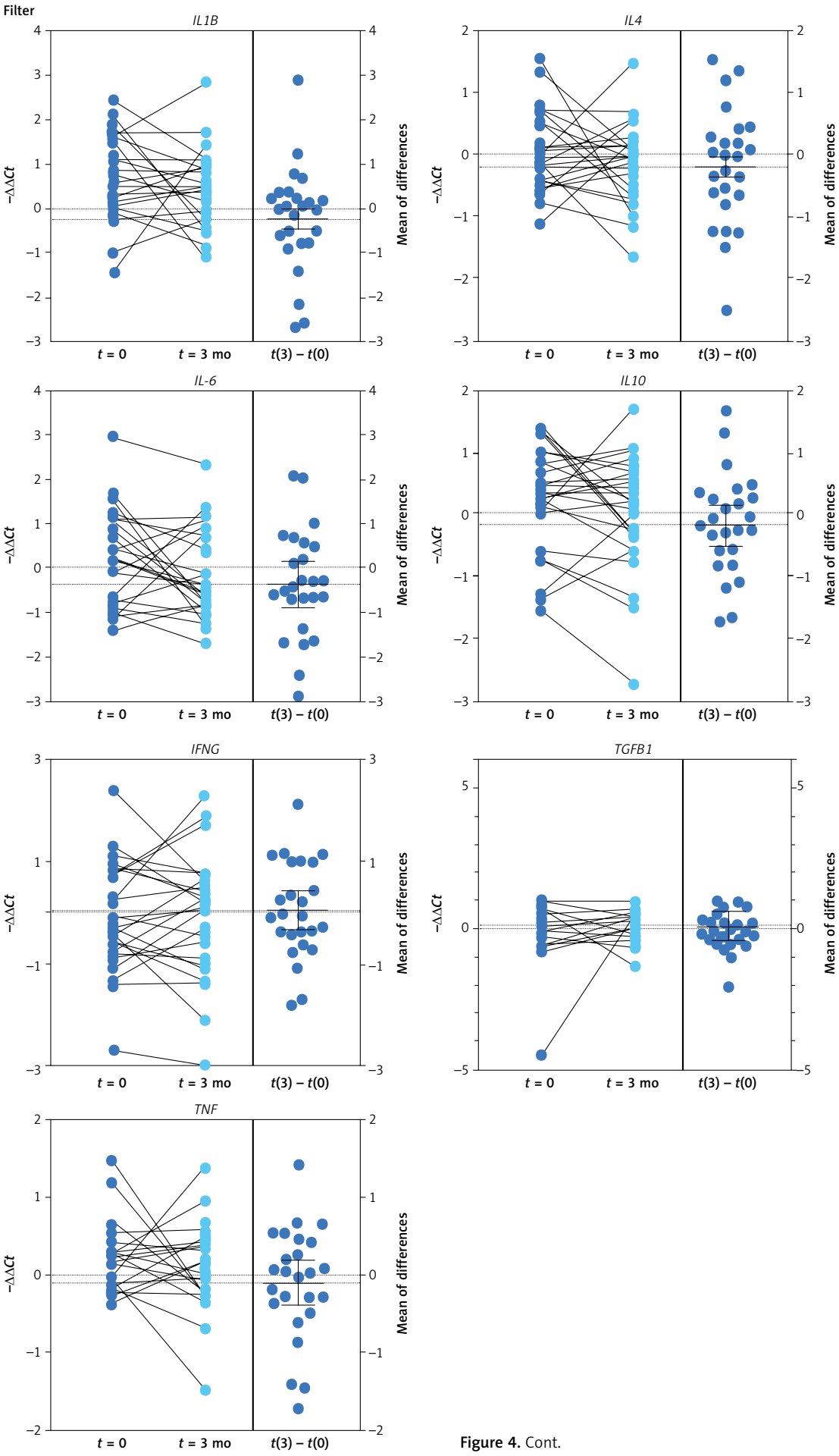


Figure 4. qRT-PCR gene expression analysis of the indicated cytokine-coding genes in PBMCs. The left section of the graphs shows the change in the individual −ΔΔCt values at $t = 0$ and $t = 3$ months in pg/ml. *36B4* was used as a loading control, and data were normalised to the mean of the tap water group prior to the intervention. $^{*}p < 0.05$ (t test). $^{\#}p < 0.05$ (two-way ANOVA). The right section of the graph shows the variation of the values for each patient with the intervention and includes the mean ± SEM



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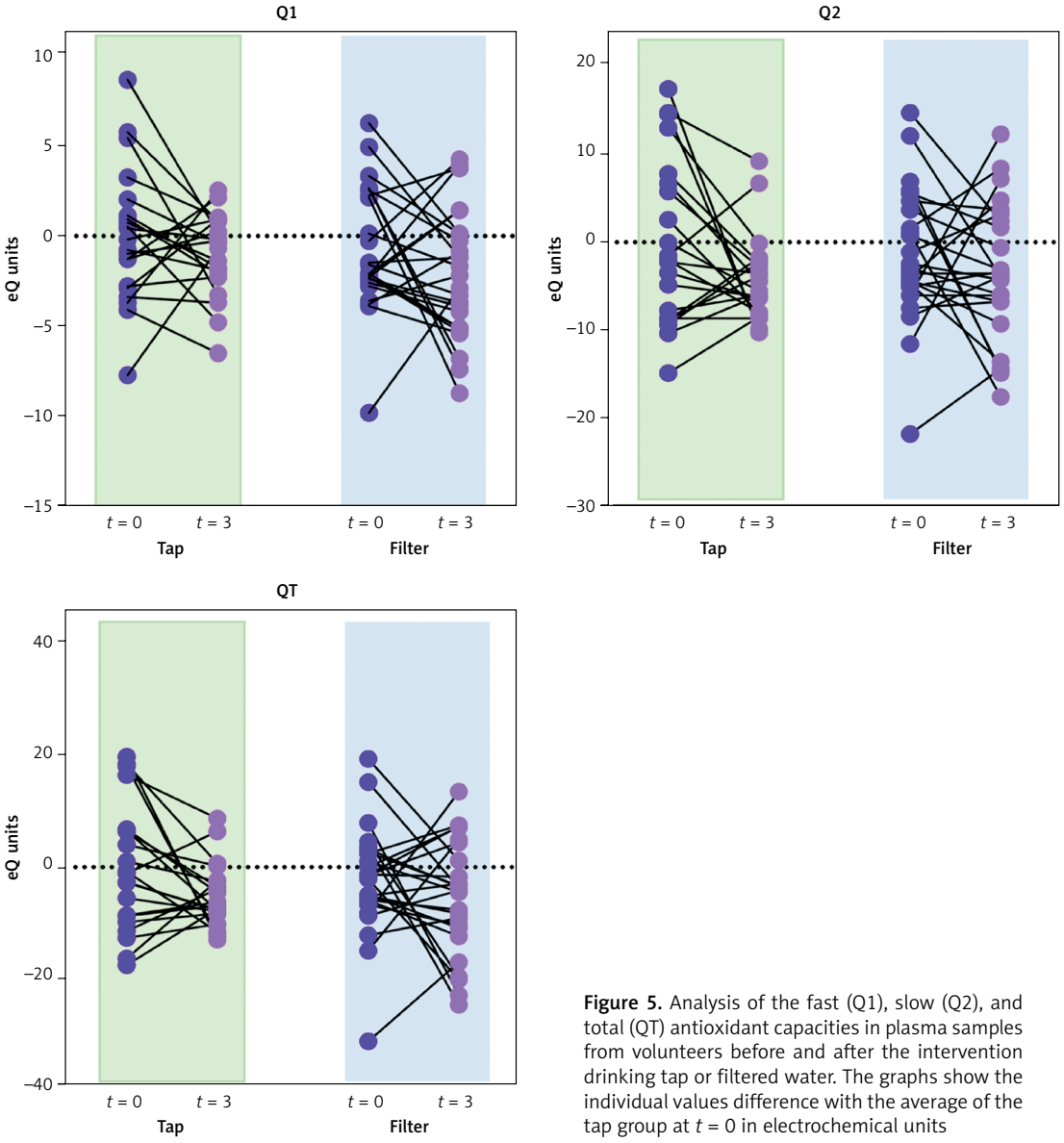


Figure 5. Analysis of the fast (Q1), slow (Q2), and total (QT) antioxidant capacities in plasma samples from volunteers before and after the intervention drinking tap or filtered water. The graphs show the individual values difference with the average of the tap group at $t = 0$ in electrochemical units

(Reference number: 050501200065), the Spanish Research Agency MCIN/AEI grants PID2021-122765OB-I00, PID2024-159721OB-I00, and by the EU Horizon Europe Program under the EIC Pathfinder grant DiBaN GA-101162517.

Ethical approval

Approval number: 044/2021.

Conflict of interest

The authors declare no conflict of interest.

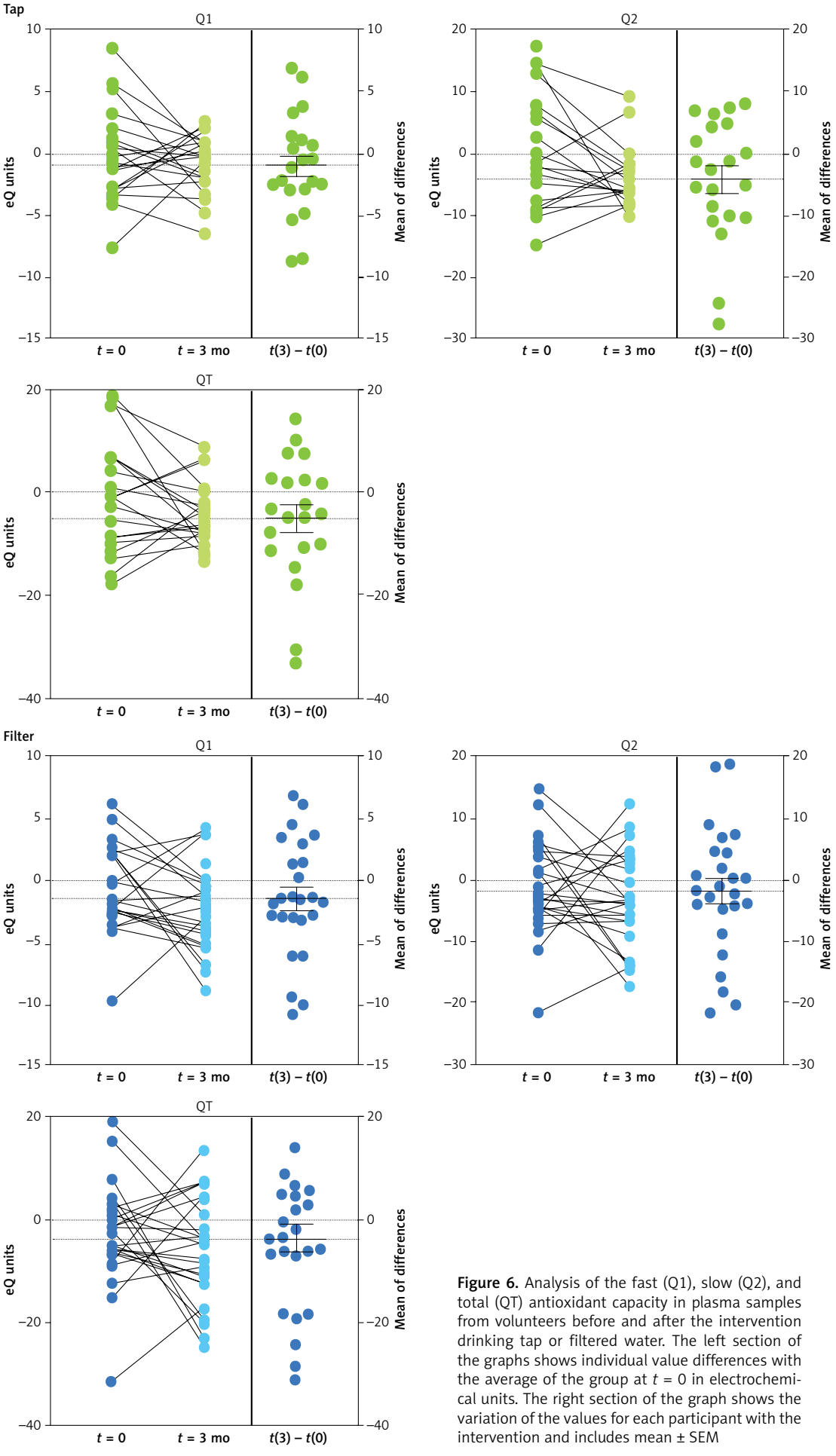


Figure 6. Analysis of the fast (Q1), slow (Q2), and total (QT) antioxidant capacity in plasma samples from volunteers before and after the intervention drinking tap or filtered water. The left section of the graphs shows individual value differences with the average of the group at $t = 0$ in electrochemical units. The right section of the graph shows the variation of the values for each participant with the intervention and includes mean ± SEM

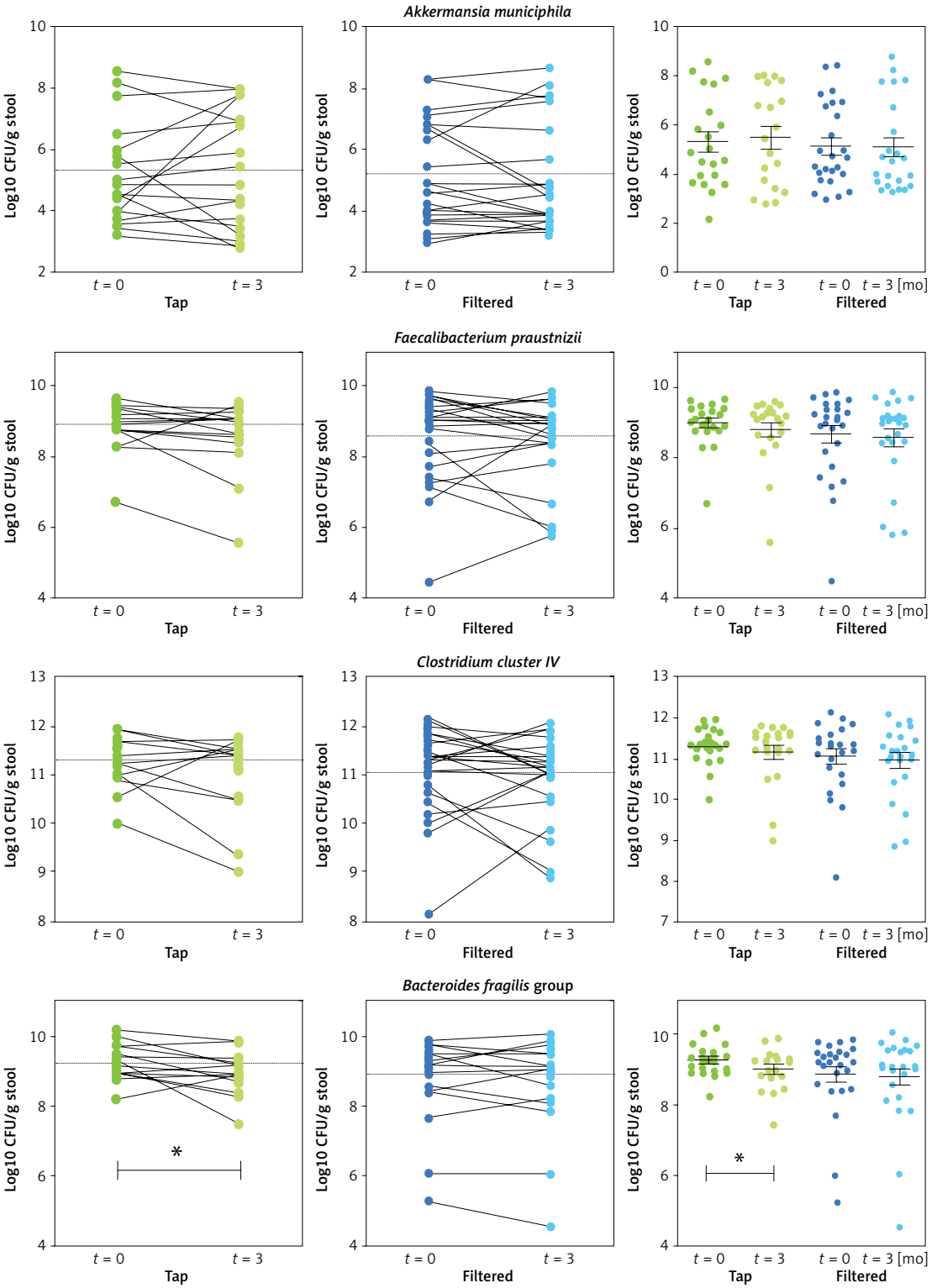
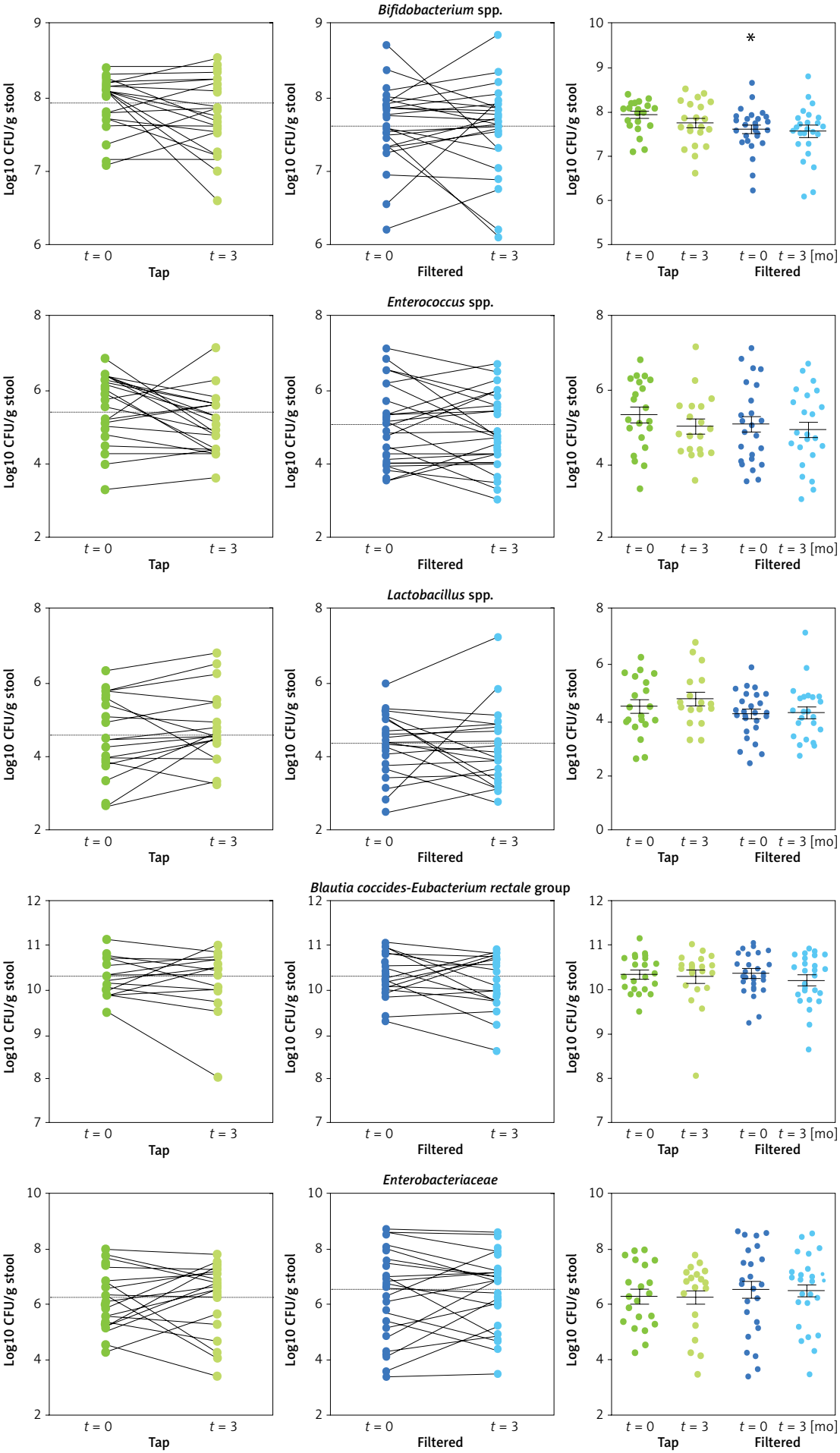


Figure 7. qPCR analysis of faecal microbial content. The graphs on the left panels show how individual values changed according to the intervention. The right panels show the distribution of individual values prior to and after intervention, and include the mean ± SEM. Statistical comparison between groups was carried out using *t* test type 1 (variations over time) and type 2 (differences between groups). *$p < 0.05$



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