Effect of Dietary Interventions in the Gene Expression Involved in Molecular Mechanisms of Obesity: Evidence-Based Translational Research from Clinical Trials

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Abstract

Dietary interventions in humans are capable of altering the gene expression related to obesity. The mechanisms underlying the anti-obesity properties of diets and nutrients involved different metabolic pathways, such as energy expenditure, lipid metabolism, adipogenesis, inflammatory signalling, among others. These effects can be analysed through the human tissue samples and / or blood analyses, where changes in messenger RNA (mRNA) levels from genes are observed. Caloric restriction, dietary macronutrients distribution, functional food are the most studied interventions, whereas functional food appears to have a synergistic role in the treatment of obesity. In this context, further studies are needed to evaluate the interaction between functional food and dietary modifications.

Keywords: Obesity; Nutrigenomics; mRNA; Dietary Intervention; Functional Food; Gene Expression

Introduction

According to the World Health Organization (WHO) obesity is defined as a situation in which abnormal or excessive accumulation of body fat damages health [1]. The latest WHO reports indicate that in 2014 more than 600 million adults worldwide were obese and in this context, obesity is considered as the pandemic of XXI century [1]. Therefore, the increasing prevalence of obesity in both developed and developing countries, leads to consider this disease as a global public health problem [1].

Epidemiological studies have shown a relation between the incidence of obesity and the imbalance between the energy intake and energy expenditure [2]. Although, the environmental influences such as the exposure to high-fat food and physical inactivity, are mainly factors in the study of obesity, the occurrence of a genetic background may also be part of the causes of obesity [3]. In recent years, it has been developed the study of how nutrients and other food components can influence gene expression at the molecular level (nutrigenomics) [4]. In this context, several genes have been linked to cellular and molecular mechanisms involved in the development of obesity. In this

sense, the effect of nutrients and dietary modifications on the expression of genes related to metabolic diseases as obesity, has become a very complex field of research that still has many aspects to be elucidated.

Several experimental studies have been conducted in *in vitro* and animal models to understand the mechanisms by which certain target genes can be downregulated or upregulated through modifications in the dietary pattern [5]. However, nutrigenomics studies in clinical trials are lacking to date because it’s difficult to obtain samples of patients or volunteers related to nutrition studies. In this context, one of the transcriptomic method based on the study of the gene expression profile (mRNA) is the use of peripheral blood mononuclear cells (PBMC) [6]. Therefore, the expression of genes after a nutritional intervention could provide a preventive and diagnostic information. Likewise, several reports have studied the use of functional food as dietary supplements for body weight management and associated metabolic disorders. However, there are few studies that evaluate the effect of this source with bioactive compounds at the transcriptional level in clinical trials [7]. Therefore, the aim of this systematic review was to identify and analyse the different types of dietary interventions in humans on the expression of different genes related to obesity through the search for clinical trials.

**Material and Methods**

The search was performed in the Pubmed database of the recently published studies and the following search equation was conducted: Obesity AND mRNA AND ("Diet" OR "Nutrients" OR "Dietary Carbohydrates" OR "Dietary Fats" OR "Dietary Proteins" OR "Micronutrients" OR "Vitamins" OR "Functional Foods" OR "Dietary Fiber" OR "Omega 3" OR "Probiotics" OR "Polyphenols") NOT ("Exercise" OR "Drugs") with the terminology Mesh and TextWord relevant to the aim of the research. On the other hand, other filters were used: “Human” and “Clinical Trials” in order to obtain studies conducted in humans. Finally, original articles and adult population were selected to obtain 20 studies to analyse in this review. These studies had statistical methodology of multivariate analysis, which reported the links between dietary interventions and gene expression related to the development of obesity, likewise, the association with specific phenotypes for obesity such as body weight, body fat, body mass index (BMI) and molecular endophenotypes as biochemical markers of lipid metabolism, serum levels of enzymes, cytokines and others.

**Results**

Table 1 shows the studies that analysed dietary interventions on obesity gene expression in humans. The main interventions found were caloric restriction, changes in the proportion of macronutrients in the diet and some intervention studies that include functional foods such as polyphenols rich olive oil, probiotics yogurt, Omega 3, vitamin D and calcium.

<table>
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<tr>
<th>Dietary intervention / Period</th>
<th>Population Type of study</th>
<th>Samples and genes</th>
<th>Gene function</th>
<th>Results Phenotype or endophenotype</th>
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<tr>
<td>MODIFIED FAT DIETS</td>
<td>Total = 29 volunteers (17 Obese, 12 normal weight) Age: 18 to 60 Rando-mized con-trolled cros-s-over</td>
<td>Skeletal muscle and abdominal adipose tissue CB1-R (cannabinoi receptor type 1) DAGLα (diacylglycerol lipase-alpha) FAAH (fatty acid amide hydrolase) MAGL (monoacylglycerol lipase)</td>
<td>Regulation of appetite and satiety</td>
<td>Downregu-late expres-sion on CB1-R and MAGL mRNA levels in skeletal muscle</td>
<td>Serum levels of endocannabi-noids were not affected</td>
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</tbody>
</table>

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<th>Total Volunteers</th>
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<td>Very low-calorie diet (VLCD), low-calorie diet (LCD) and maintenance diet (MD)</td>
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<td>VLCD for 1 month, LCD for 2 months, MD for 3 months</td>
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</table>

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<table>
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<tr>
<th>VLCD for 2 weeks</th>
<th>12 obese women with type 2 diabetes mellitus (T2DM), 8 non-diabetic obese women, 15 healthy women</th>
<th>Randomized</th>
<th>Adipose tissue and PBMC Chemokine and cytokine receptors</th>
<th>Cellular inflammation</th>
<th>Downregulate expression on 39 genes involved cellular inflammation</th>
<th>No changes in cytokine circulating levels</th>
<th>[14]</th>
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<tr>
<td>VLCD for 2 weeks</td>
<td>17 non-diabetic obese women, 14 obese women with T2DM</td>
<td>Cross-sectional</td>
<td>PBMC (blood) Macrophage inhibitory cytokine (MIC1)</td>
<td>Cellular inflammation</td>
<td>Downregulate expression on MIC1 in non-diabetic obese women</td>
<td>Decreased BMI, body fat percentage and serum levels of cholesterol and triglycerides</td>
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<td>Cross-sectional</td>
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<td>Downregulate expression on Apelin and apelin receptor</td>
<td>Decreased BMI, plasma insulin, apelin and TNFα</td>
<td>[16]</td>
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<tr>
<td>VLCD for 1 month and stabilization diet for 5 months</td>
<td>Total = 27 obese women Age: 28 ± 1</td>
<td>Prospective cross-sectional</td>
<td>Adipose tissue CD163 and CD68</td>
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<td>Upregulate expression on CD163</td>
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<tr>
<td>FUNCTIONAL FOODS</td>
<td>Probiotics for 8 weeks LCD and yogurt</td>
<td>Total = 75 volunteers with overweight and obesity</td>
<td>Double-blind clinical trial</td>
<td>PBMC (blood) TNFα and RAR receptor</td>
<td>Inflammation and oxidative stress</td>
<td>Downregulate expression on RAR receptor in LCD and probiotics yogurt</td>
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<tr>
<td>Probiotics for 8 weeks LCD and probiotics yogurt</td>
<td>Probiotics yogurt</td>
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<td>Probiotics yogurt</td>
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<tr>
<td>Probiotics for 8 weeks LCD and yogurt</td>
<td>Total = 75 volunteers with overweight and obesity</td>
<td>Double-blind clinical trial</td>
<td>PBMC (blood) FOXP3, T-bet, GATA3, TNFα, IFNγ, TGF-β</td>
<td>Inflammation and oxidative stress</td>
<td>Downregulate expression on T-bet in probiotics yogurt groups and IFNγ in the three groups</td>
<td>Body weight loss</td>
<td>[19]</td>
</tr>
<tr>
<td>LCD and probiotics yogurt</td>
<td>Probiotics yogurt</td>
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</tbody>
</table>

### Effect of Dietary Interventions in the Gene Expression Involved in Molecular Mechanisms of Obesity: Evidence-Based Translational Research from Clinical Trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Participants</th>
<th>Study Design</th>
<th>Gene Expression</th>
<th>Pathway</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>B-D glucans for 4 weeks</td>
<td>12 volunteers with overweight and obesity (4 men and 8 women) Age: 49.7 ± 3.9</td>
<td>Double-blind clinical trial</td>
<td>Interleukin 10 (IL10)</td>
<td>Cellular inflammation</td>
<td>Upregulate expression on IL-10 (anti-inflammatory)</td>
<td>Increased levels of IL-10 in blood</td>
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<tr>
<td>Omega 3 for 12 weeks</td>
<td>Total = 33 volunteers (22 women and 11 men) Age: 53.9 ± 10.9</td>
<td>Double-blind clinical trial</td>
<td>PBMC (blood) Monocyte chemoattractant protein-1 (MCP1)</td>
<td>Immune response associated with obesity</td>
<td>Downregulate expression on MCP1</td>
<td>Decreased MCP1 plasma levels</td>
</tr>
<tr>
<td>Low-fat yogurt supplemented with Omega 3, polyphenols and L-carnitine for 12 weeks</td>
<td>Total = 42 volunteers (13 women, 29 men) Age: 53.9 ± 10.9</td>
<td>Double-blind clinical trial</td>
<td>PBMC (blood) PPARα and target genes (CPT1A, CPT1B, OCTN2-carnitine transporter)</td>
<td>Lipid metabolism</td>
<td>Upregulate expression on PPARα and target genes (CPT1B, CPT1A, OCTN2)</td>
<td>Decreased fatty acids and triglycerides plasma levels</td>
</tr>
<tr>
<td>Oral treatment with 7000 IU of vitamin D</td>
<td>Total = 94 obese volunteers</td>
<td>Double-blind clinical trial</td>
<td>Subcutaneous adipose tissue MCP1, IL6, IL8</td>
<td>Cellular inflammation</td>
<td>No results</td>
<td>No changes in anthropometric parameters (BMI, waist-hip circumference, total body fat)</td>
</tr>
<tr>
<td>Analogues of vitamin D</td>
<td>Total = 94 obese volunteers</td>
<td>Double-blind clinical trial</td>
<td>PBMC (blood) PPARγ, PGC1α</td>
<td>Cellular inflammation</td>
<td>Upregulate expression on PPARγ and PGC1α</td>
<td>Decreased TNFα, IL6, IL10 and 25-hydroxy vitamin D circulating levels</td>
</tr>
<tr>
<td>Supplements with ephedrine and caffeine for 4 weeks</td>
<td>Total = 13 obese women Age: 25 – 52</td>
<td>Double-blind clinical trial</td>
<td>Rectus abdominis muscle UCP3</td>
<td>Energy expenditure</td>
<td>No significant changes in mRNA levels</td>
<td>Body weight loss, increased resting metabolic rate (RMR)</td>
</tr>
<tr>
<td>Postprandial Metabolism Polyphenols rich olive oil in the postprandial state (4h)</td>
<td>Total = 20 volunteers with obesity (9 men, 11 women) Age: 40 to 70</td>
<td>Double-blind clinical trial</td>
<td>PBMC (blood) Genes related with inflammatory processes</td>
<td>Cellular inflammation</td>
<td>98 differentially expressed genes (79 downregulated and 19 upregulated)</td>
<td>No changes in clinical parameters</td>
</tr>
</tbody>
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<table>
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<tr>
<th>4 kind of breakfast prepared with different oils (olive oil, sunflower oil, and a mixture of seed oils with antioxidants)</th>
<th>Total = 20 obese volunteers</th>
<th>Cross-sectional</th>
<th>PBMC (blood) NFKB and other inflammatory molecules (TNFα, IL1β, IL6)</th>
<th>Cellular inflammation</th>
<th>Olive oil and seed oil with antioxidants down-regulate expression of pro-inflammatory genes and sunflower oil, upregulate expression.</th>
<th>Decreased TNFα, IL6, IL1β plasma levels</th>
<th>[27]</th>
</tr>
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<tbody>
<tr>
<td>Breakfast based on 4 types of olive oil with high, medium and low polyphenol content</td>
<td>Total = 49 volunteers with metabolic syndrome (19 men and 30 women)</td>
<td>Single-blind randomized clinical trial</td>
<td>PBMC (blood) NFKB, IL6, IL1β</td>
<td>Cellular inflammation</td>
<td>The olive oil high polyphenols downregulate expression on NFKB, IL6, IL1β compared with other oils</td>
<td>No changes in clinical parameters</td>
<td>[28]</td>
</tr>
</tbody>
</table>

**Table 1: Dietary intervention studies and the anti-obesogenic effect in clinical trials.**

In this context, the main genes affected by changes in dietary pattern in obese individuals were those associated with energy expenditure (α2-AR, β2-AR, UCPs), cellular inflammation (interleukins, adipokines and chemokines MCP1, PGC1α, ROR, NFKB, MAPK), lipid metabolism (PPARy, CPT1A, CPT1B, GPR41, GPR43, HSL, ATGL) and appetite regulation and food intake control (FAAH, CB1Rs) (Figure 1) [8].

**Figure 1:** Obesity-related genes that can be altered after different types of dietary interventions.

Energy expenditure

The total energy expenditure represents the energy that the body uses and is constituted by the sum of the basal metabolic rate, endogenous thermogenesis (ET) and physical activity (PA) [29]. Obesity is caused by a prolonged imbalance between caloric intake and energy expenditure [30]. There are powerful homeostatic mechanisms to maintain body weight, similarly to other biological constants, such as body temperature, however in pathological situations such as obesity, the ability to regulate the system is exceeded and its effectiveness decrease significantly. Some authors have observed a reduction in the metabolic rate during caloric restriction programs, suggesting that the body tends to compensate for the low-calorie intake, however, this metabolic process is not yet clearly understood [8]. On the other hand, thermogenesis not only depends on the supply of nutrients, but also the specific regulation of its use through endocrine processes and genetic factors [30].

In this sense, activation of β-adrenergic receptors are mainly related to the regulation of lipolysis and thermogenesis in White and Brown Adipose Tissue (WAT) and (BAT) [30]. Thus, Koppo, et al. [12] reported an upregulation of β2-AR gene expression (lipolysis) and downregulation of α2-AR (antilipolytic) mRNA levels in subcutaneous adipose tissue after a caloric restriction program in 15 obese premenopausal women. Likewise, there was a reduction in mRNA levels of hormone sensitive lipase (HSL) and adipocyte triglyceride lipase (ATGL) after caloric restriction treatment for 10 weeks [12].

Uncoupling proteins (UCPs) represent a family of mitochondrial proteins that promote the translocation of protons from the intermembrane space to the mitochondrial matrix. The UCPs roles in humans are being studied and recent evidence suggests that they are involved in thermogenesis, regulation of ATP synthesis, control of oxidative stress and fatty acids and glucose metabolism [25]. In 2014, Bracale, et al. [25] conducted a study with 13 premenopausal morbidly obese women and supplemented with ephedrine and caffeine for 4 weeks. Changes in UCP3 gene expression in skeletal muscle and energy expenditure were studied and found a thermogenic effect and body weight loss in the volunteers after the treatment. However, this results were not associated with changes in the gene expression suggesting other physiological mechanisms involved [25].

Cellular inflammation

In recent years, it has been described that the growth of the adipose tissue not only increases macrophages, but also causes a change in the polarization of macrophages from M2 to M1, leading from anti-inflammatory profile to proinflammatory status, that could be responsible for the expression of most of the proinflammatory cytokines produced in the adipose tissue and the molecules involved in the recruitment of more macrophages in the tissue. In this context, a vicious cycle is established with increasing activation of the inflammatory pathways [31].

Camargo, et al. [26] identified changes in the expression of genes related to pathways of cellular inflammation in peripheral mononuclear blood cells, after offering a polyphenol rich olive oil to 20 obese adults (4 h postprandial state). In this study, microarray analyses were conducted and 79 genes related to proinflammatory processes decrease the mRNA expression. Prostaglandin-endoperoxide synthase 2 (PTGS2) is a key cyclooxygenase involved in the biosynthesis of prostaglandins using arachidonic acid as substrate and in the decrease expression of genes related with chemokines and their receptors responsible for recruitment and activation macrophages during the inflammatory response. Evidence suggests that these molecular mechanisms have a great influence on chronic cellular inflammation, the pathological basis of obesity [26].

On the other hand, Mraz, et al. [14] performed a study with obese women with and without diabetes mellitus and evaluated the effect of a very low calorie-diet for 2 weeks on the expression of genes involved in cellular inflammation. Thus, they reported that the short period of caloric restriction was able to significantly decrease the chemokine mRNA levels and cytokine receptors in a peripheral mononuclear blood cells. This results could subsequently reduce the recruitment of monocytes into adipose tissue, partially explaining a positive anti-inflammatory effect after the dietary intervention [14].

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Lipid metabolism and adipogenesis

Genes related to the regulation of cell growth and adipocyte differentiation can be considered as target genes for the regulation of body weight [8]. Fatty acids, especially long chain and unsaturated, enhance peroxisome of proliferator-activated receptor (PPAR) expression in adipose tissue. PPARs are transcription factors that regulate lipid metabolism such as fatty acid oxidation, adipogenesis and insulin sensitivity [8].

Radler, et al. [22] evaluated the effect of low-fat yogurt enriched with Omega 3, L-carnitine and antioxidants (polyphenols, vitamin C and vitamin E) for 12 weeks. PPARα, CPT1A (carnitine palmitoyl transferase 1A), CPT1B (1B carnitine palmitoyl transferase), CrAT (carnitine acetyltransferase 2) were upregulated after the nutritional treatment. In this context, the expression of these genes is related with lipid-lowering effects through increased beta-mitochondrial oxidation of free fatty acids. These mechanisms leads an increase production of reactive oxygen species from the electron transport chain [22]. Therefore, the addition of antioxidants are necessary to suppress the synthesis of these oxidative substances. In this context, the combination of the nutritional treatment with omega 3, carnitine and antioxidants, causes a synergistic effect on decreasing plasma lipids through the modulation of lipolytic gene expression [22].

Van Hees, et al. [11] determined the contribution of the amount and composition of dietary fat on the expression of lipolytic genes in the subcutaneous adipose tissue of 32 obese volunteers. After 4 different type of diets (high saturated fat diet; high monounsaturated fat diet; low fat and high carbohydrate supplemented with and without omega 3), there were no changes in the expression of HSL and ATGL genes. On the other hand, changes in protein synthesis were observed in volunteers with low-fat and high carbohydrate diet suggesting a possible post-transcriptional regulation mainly through activation mechanisms such as phosphorylation, translocation or interaction with other proteins [11].

Appetite and food intake

The brain plays an important role in maintaining energy homeostasis [32]. In this sense, the role of the hypothalamus and other systems related to food intake were studied in relation to body weight control [32]. Leptin is encoded by the leptin gene (LEP) and secreted by white adipose tissue, acting through the leptin receptor (LEPR) to regulate satiety, energy expenditure, immune system and inflammatory response, lipid and carbohydrate metabolism, and the intestinal absorption of nutrients among other processes [8].

Meanwhile the endocannabinoid system is also a target as a regulatory of food intake. Two endocannabinoid substances have been investigated in human intervention studies: FAAH, the main enzyme responsible for the inactivation of the ligands endogenous cannabinoids receptors and the protein encoded by CNR2 which is involved in exerting effects at the central nervous system levels [8].

Engeli, et al. [9] studied the effect of increasing dietary fat intake on gene expression of endocannabinoids in 12 obese and 17 healthy volunteers. Nevertheless, no changes were found on mRNA levels suggesting no effects on food intake after dietary fat consumption in an isocaloric dietary intervention.

Discussion

Transcriptomics is one of the 3 omics sciences that focuses on the study of the transcriptome (messenger RNA produced from genomic DNA). This science has been considered one of the most appropriate to evaluate the effect of diet on gene expression (nutrigenomics) [32]. In this sense, microarrays technique analyses the expression of thousands of genes in different samples. The use of the peripheral blood mononuclear cells has a promising role in the field of nutritional genomics, since they are most accessible and a non-invasive technique [6].

Throughout the reviewed studies, it is observed that some types of changes in dietary pattern (e.g. caloric restriction), and the inclusion of some functional foods (polyphenols rich olive oil) are able to modify common genes related with obesity and the mechanisms involved the development of the disease, such as cellular inflammation [14,26]. In this context, understanding how nutrients affect the
expression of genes, it is possible to propose studies that evaluate the effectiveness of a dietary pattern (caloric restriction diet or modified in macronutrients and supplemented with a functional food) as an alternative to increase the positive effects on obesity.

Additionally, most of the investigations focus on studying the expression of candidate genes associated with obesity. Obesity is a complex and polygenic disease, therefore future studies are needed to evaluate the impact of diet on a greater number of genes as a strategy to detect genes that can also be modified after dietary intervention and possible playing a key role in the pathophysiology of the disease [33]. In fact, the use of microarrays technique is recommended, however high costs and scarce availability of this type of technology are frequent limitations to generate this type of studies [8].

In some studies, there were no changes in gene expression after dietary interventions [23,25]. Although there are in vitro and animal studies that support the theoretical foundation of the effectiveness of treatments, changes in phenotypes or endophenotypes can be found without changes in target genes [25]. Furthermore, the changes in biological activity found may be due to the modification of some other genes not studied.

On the other hand, the period of treatment is an important variable to consider in this studies. Some studies were conducted as a very short intervention period and there were no changes at the transcriptional levels. Other studies have analysed the expression of genes at the postprandial level [34].

In summary, future clinical trials were needed to evaluate the nutrigenomic impact of novel functional foods proposed as alternatives in the treatment of obesity, especially those that modulate the expression of genes related with the appetite and food intake (LEP, LEPR, endocannabinoids, ghrelin).

**Conclusion**

Studies of dietary interventions in humans are necessary as a translational research in nutrigenomics approach. Many in vitro and animal models obtain results to explain at the molecular level the effect of different nutrients on target genes related to metabolic diseases to contribute to understand the pathology and the nutrition treatments.

Likewise, it is necessary to perform studies on the genetic basis of postprandial metabolism as an approach with less uncontrollable variables that can alter the changes in gene expression.

Finally, it is recommended that future studies include the 3 omics sciences (transcriptomics, proteomics and metabolomics) in order to have more comprehensive view of what happens after a nutrigenomics intervention, from the approach of Biology Systems.

**Conflict of Interest**

No conflicts of interests have been declared by any of the authors.

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