Serum visfatin concentrations are positively correlated with serum triacylglycerols and down-regulated by overfeeding in healthy young men

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ABSTRACT

Background: Visfatin is an insulin-mimicking adipokine. Visfatin is elevated in obesity and type 2 diabetes. However, its role in glucose and lipid metabolism in healthy humans is unclear.

Objective: The objective was to investigate the correlations of visfatin with phenotypes of glucose, lipids, and body composition and the responses of visfatin to short-term overfeeding in healthy young men.

Design: Fifty-one healthy young men were recruited from the Newfoundland population. Serum visfatin, interleukin 6, glucose, insulin, total cholesterol, HDL cholesterol, LDL cholesterol, and triacylglycerol concentrations were measured with an autoanalyzer, and percentage body fat (%BF) and percentage trunk fat (%TF) were measured with dual-energy X-ray absorptiometry. Insulin resistance and β cell function were assessed with the homeostasis model. All measurements were completed at baseline and after a 7-d overfeeding protocol exceeding the baseline requirement by 70%. Subjects were classified on the basis of %BF as lean (<21%), overweight (21–25.9%), or obese (≥26%).

Results: Multiple regression analysis showed that triacylglycerols correlated with fasting serum visfatin (P < 0.001). Moreover, serum visfatin decreased 19% overall—23% in lean, 9% in overweight, and 18% in obese subjects (P < 0.0001)—after the overfeeding protocol. None of the variables measured, including interleukin 6, were associated with the reduction in visfatin. In contrast with the findings in mice, visfatin concentrations before and after overfeeding did not correlate with glucose, insulin, insulin resistance, β cell function, %BF, or %TF.

Conclusions: Visfatin is down-regulated by overfeeding. Under physiological conditions, visfatin does not appear to control glucose metabolism but may play a regulatory role in lipid metabolism.


KEY WORDS Visfatin, insulin resistance, lipids, body composition, nutritional regulation

INTRODUCTION

Visfatin, also called pre-B cell colony-enhancing factor 1 (PBEF1), is a novel adipokine that is secreted by visceral and subcutaneous fat, human bone marrow, liver, and muscle (1–4). PBEF1 was primarily considered a factor related to the pre-B cell colony-formation activity of stem cells and was therefore defined as a cytokine, which acts on early B lineage precursor cells (4).

PBEF1, now known as visfatin, has a calculated molecular mass of 52 kDa with deduced 473 amino acids (4) and was recently shown to be involved in the development of obesity-associated insulin resistance and type 2 diabetes mellitus in human and animal models (1, 3). The concentration of visfatin in plasma increases during the development of obesity, and it was shown to exert insulin-mimetic effects in cultured myocytes and adipocytes and to lower plasma glucose concentrations in mice (1). Furthermore, plasma visfatin was also found to be elevated in patients with type 2 diabetes (3). Insulin resistance and deficiency of β cell function are 2 principal characteristics of type 2 diabetes mellitus. Evidence from animal and in vitro experiments suggests that visfatin is one of the factors involved in the complex network that controls insulin resistance.

Although visfatin showed insulin-like function in mice, it is unclear how it relates to insulin resistance–related phenotypes in humans because previous studies showed an inconsistency of adipokine function between humans and rodents (5). As well, it is not known whether serum visfatin concentrations are correlated with the amount of body fat in healthy people as observed in mice. Changes in nutritional status such as overfeeding, underfeeding, and exercise have important effects on adipose tissue metabolism (6, 7) and may affect visfatin concentrations. Although visfatin is considered to be a link between obesity and diabetes (8), to date, data related to the nutritional regulation of visfatin are lacking.

The information obtained from examining the response to these nutritional changes will provide insight into the mechanisms and roles of this adipokine in obesity and the metabolic syndrome (9). In this study, we investigated the relation of fasting serum visfatin concentrations at baseline and in response to a short-term overfeeding with the phenotypes of glucose, lipids, and body compositions in healthy young men.

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Received June 23, 2006.
Accepted for publication September 12, 2006.

SUBJECTS AND METHODS

All subjects were recruited from the St John’s area of the Canadian province of Newfoundland and Labrador. A total of 61 young men participated in the study. Healthy young men are often selected in overfeeding studies because they can tolerate overfeeding better than older subjects, and the potential risk caused by overfeeding would be small (10–12). Subjects who met the following criteria were eligible to participate in the study: 1) male; 2) aged 19–29 y; 3) at least a third-generation Newfoundland; 4) healthy with no serious metabolic, cardiovascular, or endocrine diseases; 5) not taking medication for lipid metabolism; and 6) reporting a stable weight (±2.5 kg) within the previous 6 mo. All subjects provided written consent, and the Ethical Committee of the Faculty of Medicine, Memorial University of Newfoundland, approved the study.

Serum measurements

Blood samples were taken from all subjects, after they had fasted overnight for 12 h, before and after completion of the overfeeding study. Serum was stored at −80 °C for subsequent analyses. Serum visfatin concentrations were measured in duplicate with a human visfatin (COOH-terminal) enzyme immunoassay (Phoenix Pharmaceuticals, Belmont, CA) performed on an Alisei Quality System (SEAC Radim Group, Pomezia, Italy). Assay sensitivity was 2 ng/mL, and interassay and intraassay CVs were <10% and <5%, respectively. Serum interleukin 6 (IL-6) concentrations were measured in duplicate with the use of the Access IL-6 kits (Beckman Coulter Inc, Fullerton, CA) performed on a Unicel Dxl 800 Access Immunoassay system (Beckman Coulter Inc). Serum concentrations of glucose, triacylglycerol, total cholesterol, and HDL cholesterol were measured with the use of Synchron reagents and performed on an Lx20 analyzer (Beckman Coulter Inc). LDL cholesterol was calculated with the use of the following formula: (total cholesterol) – (HDL cholesterol) – (triacylglycerols/2.2). The calculated value is reliable in the absence of severe hyperlipidemia. Serum insulin concentrations were measured on an Immulite immunoassay analyzer (DPC, Los Angeles, CA). The homeostasis model assessment (HOMA) was used as a measure of insulin resistance [HOMA-IR = insulin (μU/mL) × glucose (mmol/L)/22.5] and β cell function [HOMA-β = 20 × insulin (μ U/mL)/(glucose − 3.5)] (13).

Measurement of body composition

Total percentage body fat (%BF) and percentage trunk fat (%TF) were determined with the use of dual-energy X-ray absorptiometry (DXA) LunarProdigy (GE Medical Systems, Madison, WI). Although %BF and %TF are highly correlated, %TF represents visceral fat better than does %BF. Measurements were performed on subjects after the removal of all accessories containing metal, while lying in a supine position as previously described (14). Software version 4.0 was used for analysis. All measurements were performed before overfeeding and the day after overfeeding.

Overfeeding protocol

In previous studies, both short-term and long-term overfeeding strategies were used to investigate biochemical and metabolic responses (15–24). Most overfeeding studies are short term, ranging from 12 h to 22 d. Overfeeding has a rapid effect on gene expression. In one study, insulin receptor mRNA concentrations began to decrease in 30 min, and acetyl-CoA carboxylase and fatty acid synthase mRNA concentrations began to increase in human adipose tissue 4–8 h after feeding (25). This study followed a 7-d overfeeding protocol to ensure that the intervention would induce expression changes in adipose tissue genes. Overfeeding studies can also be classified as mixed, high-fat, high-carbohydrate, and protein diet overfeeding (16, 17). We used a mixed diet to mimic the common daily diet in North America. In previous studies, the amount of overfeeding varied from 30% to 100% above normal energy requirements (16, 17, 20, 23, 24). Seventy percent was chosen for this study.

Subjects first underwent baseline energy intake assessments, which included three 24-h diet recalls and completion of a 30-d dietary inventory (26). Total energy expenditure was estimated by an Actical physical activity level monitor (Mini Mitter Co, Inc, Bend, OR). Individual baseline energy requirements were estimated with the use of an average of three 24-h recalls and a 30-d dietary inventory. Subjects were then started on a 70% hypercaloric diet for 7 d (days 1–7). The macronutrient compositions of the diets were kept stable at 50% carbohydrate, 35% fat, and 15% protein. All meals were purchased from restaurants, including McDonald’s, Extreme Pita, Tim Horton’s, Swiss Chalet, Wendy’s, A&W, Dairy Queen, Kentucky Fried Chicken, Subway, and Pizza Hut, for which the nutritional information of the food supplied was available. The average intakes per day were as follows: energy (baseline: 2969 kcal; overfeeding: 5471 kcal), protein (baseline: 106 g; overfeeding: 178 g), carbohydrates (baseline: 394 g; overfeeding: 713 g), fiber (baseline: 19 g; overfeeding: 33 g), total fat (baseline: 105 g; overfeeding: 221 g), saturated fat (baseline: 38 g; overfeeding: 71 g), and cholesterol (baseline: 304 mg; overfeeding: 735 mg). Food was presented to the subjects every day for breakfast at 0900, lunch at 1200, and supper at 1700. A laboratory member was present during every meal to ensure that all food was consumed. Subjects were asked to maintain their usual pattern of physical activity. Daily physical activity levels 7 d before and during the overfeeding period were measured and compared. The variation of physical activity levels between baseline and the overfeeding period were controlled below 15%. Subjects were instructed to abstain from any alcoholic or additional calorie-containing beverages during the study period. The energy values and macronutrient content of the subjects’ intakes were computed with the use of the FOOD PROCESSOR SQL, version 9.5.0.0 (ESHA Research, Salem, OR).

Statistical analysis

Data are presented as means ± SE unless otherwise stated. Before statistical analysis, data obtained that were not normally distributed were logarithmically transformed to approximate a normal distribution for subsequent analysis (concentrations of triacylglycerol, insulin, serum visfatin, and IL-6; HOMA-IR; and HOMA-β at baseline and the changes after overfeeding). To investigate the effect of adiposity on visfatin concentration, subjects were classified according to adiposity; %BF was used to define adiposity instead of body mass index (in kg/m²) because of the increased accuracy of this method. The men aged 20–39 y were classified as obese if their BF was ≥26%, lean if <21%, and overweight if 21–25.9% (27).
TABLE 1
Changes in response to 7 d of positive energy balance induced by overfeeding in 61 men grouped by adiposity status

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lean (n = 24)</th>
<th>Overweight (n = 14)</th>
<th>Obese (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>23.0 ± 0.5</td>
<td>21.8 ± 0.8</td>
<td>22.7 ± 0.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>79.7 ± 1.3</td>
<td>179.5 ± 1.2</td>
<td>179.4 ± 1.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.6 ± 2.2</td>
<td>77.8 ± 1.1</td>
<td>93.0 ± 3.3</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>13.7 ± 0.83</td>
<td>22.5 ± 0.2</td>
<td>31.4 ± 1.0</td>
</tr>
<tr>
<td>Trunk fat (%)</td>
<td>15.5 ± 0.9</td>
<td>25.4 ± 0.5</td>
<td>35.2 ± 1.1</td>
</tr>
<tr>
<td>Visfatin (ng/mL)</td>
<td>29.3 ± 3.3</td>
<td>25.5 ± 6.6</td>
<td>-2.42 ± 3.74</td>
</tr>
<tr>
<td>IL-6 (ng/mL)</td>
<td>1.03 ± 0.32</td>
<td>1.32 ± 0.33</td>
<td>-0.45 ± 0.31</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.0 ± 0.1</td>
<td>-0.24 ± 0.25</td>
<td>5.1 ± 0.1</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>45.2 ± 4.7</td>
<td>82.0 ± 25.0</td>
<td>26.3 ± 13.1</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.3 ± 0.2</td>
<td>4.5 ± 0.3</td>
<td>0.09 ± 0.22</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0.91 ± 0.06</td>
<td>0.93 ± 0.11</td>
<td>0.02 ± 0.04</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.36 ± 0.05</td>
<td>1.35 ± 0.09</td>
<td>0.05 ± 0.06</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.51 ± 0.14</td>
<td>2.73 ± 0.25</td>
<td>-0.008 ± 0.20</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.41 ± 0.15</td>
<td>2.72 ± 0.95</td>
<td>0.79 ± 0.36</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>85.8 ± 7.9</td>
<td>133.6 ± 24.8</td>
<td>67.2 ± 40.4</td>
</tr>
</tbody>
</table>

Baseline values for percentage body fat, glucose, insulin, HOMA-IR, HOMA-β, and IL-6.

1 All values are ± SE. IL-6, interleukin 6; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-β, homeostasis model assessment for β cell function; NA, not available. Significance of changes (values after overfeeding — values at baseline) from all subjects were assessed by general linear model (GLM) with baseline values as covariate. Adiposity was not a significant factor for any variable tested.

The analysis strategy was as follows:

1) Comparisons of physical and biochemical characteristics between the 3 groups were completed with the use of one-factor analysis of variance with Bonferroni correction.
2) The analyses of the changes before and after the overfeeding protocol were tested with the use of the general linear model. The differences between lean, overweight, and obese groups were tested with the general linear model procedure by including the baseline values as covariates in the same model. Multiple comparison adjustments were performed with a post hoc Tukey's test.
3) Pearson’s correlation analyses were performed to screen potential factors related to fasting serum concentrations of visfatin. Multiple regression analyses were used to examine the predictors of fasting serum concentrations of visfatin. Variables included in various models were age, %BF, glucose, insulin, triacylglycerols, HOMA-IR, HOMA-β, and IL-6. Baseline data and the change in variables after the 7-d overfeeding were analyzed.

The SPSS version 12.0 (SPSS Inc, Chicago, IL) was used for all analyses. Statistical analyses were two-sided, and a P value < 0.05 was considered to be statistically significant.

RESULTS

Comparison of characteristics at baseline

Physical and biochemical characteristics of the subjects grouped according to adiposity status at baseline are shown in Table 1. No significant differences of age and height were observed between the 3 groups. Significant differences were observed in body weight, %BF, and %TF between lean, overweight, and obese subjects. The %BF ranged from 6% to 46.4%, which represented a wide range of lean to obese subjects. No significant differences in concentrations of fasting glucose, total cholesterol, triacylglycerol, HDL cholesterol, and LDL cholesterol were observed between the 3 groups. Insulin resistance, measured by HOMA-IR, was higher in the obese subjects than in the lean subjects. β cell function, measured by HOMA-β, was higher in the obese and overweight subjects than in the lean subjects. The average fasting visfatin concentrations at baseline were 29.3 ± 3.3, 25.5 ± 6.6, and 32.7 ± 4.6 ng/mL for the lean, overweight, and obese subjects, respectively; and no significant differences were observed between the groups.

Regulation of serum visfatin by short-term overfeeding

Changes in response to the 7-d overfeeding period in 61 young men grouped according to adiposity status are shown in Table 1...
(values are given as changes from baseline). The overfeeding resulted in a significant increase in body weight in all 3 groups. On average each subject gained 2.2 kg during the 7-d period, which reached the goal of 70% overfeeding. In all 3 groups %BF and %TF were significantly increased (\( P < 0.0001 \)). Adiposity status indexed by the 3 groups was not a significant factor for the responses to overfeeding. Fasting serum concentrations of visfatin were significantly reduced after overfeeding compared with baseline concentrations by 23%, 9%, and 18% in the lean, over-weight, and obese groups, respectively, and by 19% in the entire study group. Interestingly, IL-6 concentrations were reduced in general (\( P < 0.0001 \)). The serum glucose concentration was slightly decreased but statistically significant (\( P = 0.006 \)). After overfeeding, insulin concentrations were significantly elevated in the lean (16.8 ± 4.34 pmol/L), overweight (26.3 ± 13.1 pmol/L), and obese (14.9 ± 18.6 pmol/L) groups, as well as in the entire study group (17.5 ± 8.8 pmol/L). Concentrations of total cholesterol, triacylglycerol, HDL cholesterol, and LDL cholesterol were all significantly elevated. Insulin resistance and \( \beta \) cell function were significantly elevated. No significant effect was observed from the adiposity status for all the variables analyzed. The relations between changes of visfatin with lipids and insulin resistance indicators were analyzed as well. However, no significant correlations were found. Adiposity status was not a significant factor for the changes of all variables in response to overfeeding.

**Pearson’s correlation and multiple stepwise linear regression of serum visfatin with other variables**

Pearson’s correlations were performed to investigate the possible associations between fasting serum concentration of visfatin with serum glucose, insulin, and lipids; insulin resistance; \( \beta \) cell function; and body compositions at baseline (Table 2). No significant correlations were found between serum visfatin concentration and serum concentrations of glucose or lipids or body compositions at baseline with the following exception: a positive correlation was found between serum visfatin and triacylglycerols at baseline. Multiple stepwise linear regression analyses confirmed that triacylglycerols were the only significant predictor of baseline visfatin concentrations independent of age and %BF. As well, no significant correlations were found between the changes in visfatin with the changes in other indicators after the overfeeding period.

**DISCUSSION**

The regulation of blood glucose is controlled by a large number of endocrine factors, including insulin, glucagon, and other hormones. The continuing discoveries of adipocyte-derived cytokines, including leptin, adiponectin, resistin, tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)), and IL-6 have shed light on the cause of type 2 diabetes (28–30). These adipokines provide an extensive network in which each one communicates with other adipocytes and remotely with other tissues and organs. The network is involved in multiple biological functions, including insulin resistance, lipid metabolism, and energy homeostasis, through various pathways (31, 32).

Some adipokines correlate with the amount of adiposity, such as leptin, which is positively correlated with adiposity, and adiponectin, which is negatively correlated with body mass index and %BF (32, 33). Fukuhara et al (1) reported that visfatin is predominantly secreted by visceral fat and that plasma visfatin concentration increases during the development of obesity in mice. Therefore, it is reasonable to expect an association between circulating serum visfatin concentration and trunk fat, which is a reflection of the amount of visceral fat.

The effect of obesity status on circulating visfatin concentration is controversial. Haider et al (34) found an elevated concentration of visfatin in obese subjects, whereas Pagano et al (35) found plasma visfatin was significantly lower in obese control subjects than in normal weight control subjects. In this study, we did not find any correlation between either %BF or %TF and baseline values or changes in serum visfatin. Our results suggest that the amount of body fat and trunk fat indexed by %BF and %TF does not influence the concentration of circulating visfatin in young men. Berndt et al (36) found a positive correlation between plasma visfatin concentration and %BF measured by DXA. However, no correlation was found between plasma visfatin concentration and visceral mass measured by computed tomography (36), which accurately quantifies visceral mass.

Evidence from animals suggests that visfatin is an adipokine that exerts insulin-like action. Visfatin is able to mimic insulin function and lower plasma concentrations of glucose by binding to the insulin receptor as shown in c57BL/6J mice, insulin-resistant KKAY mice, and streptozotocin-treated insulin-deficient mice (1). If visfatin exerts the same glucose-lowering function in humans at physiologic conditions as it does in mice, we can expect an association of fasting visfatin concentrations with fasting glucose concentrations. However, none of the biochemical variables associated with glucose metabolism correlated with serum visfatin concentrations at baseline or with the changes in serum visfatin in response to the overfeeding. This is consistent with the earlier findings that show no correlation of plasma visfatin with fasting plasma glucose in a heterogeneous group of white men and women (36). The absence of correlation is likely due to the low concentration of visfatin at physiologic conditions in humans, as is the norm with the >24 types of adipokines secreted by adipose tissue. The notable exceptions to this rule are leptin and adiponectin, whose correlation with adipose tissue is evident (33). In addition, our results indicate that visfatin is likely not an important regulator of glucose metabolism or insulin resistance in lean and in overweight and obese healthy young men. Other studies found that the serum concentrations of visfatin were raised in diabetic patients (3) and gestational diabetic women (37), suggesting that visfatin may act as a compensatory factor in glucose metabolism. Its low concentration at physiologic conditions results in its limited role in this metabolic process. However, in situations of impaired insulin functioning such as in type 2 diabetes and gestational diabetic women, visfatin may be elevated and may partially compensate for insulin function.

Beyond insulin regulation, visfatin was also linked with the metabolic syndrome in humans (1), although this link remains controversial. For example, Kloting et al (38) compared the concentrations of visfatin mRNA expression of visceral and subcutaneous fat between WIKO (metabolic syndrome model) rats and normal lean control subjects, finding no significant differences between the 2 lines. In contrast to this, we found that serum visfatin concentrations at baseline were positively correlated with serum triacylglycerols, independently of age and %BF. Thus, visfatin may act in a similar fashion as adiponectin, another adipokine, which was also linked with triacylglycerols in obese
and nonobese subjects (39), as well as triacylglycerol-rich lipoproteins in nonobese men (40). Our data suggest that visfatin may exert a similar yet independent role in regulating triacylglycerol metabolism in humans. The lack of association between the changes in triacylglycerols with visfatin warrant further study. Because elevated serum triacylglycerols is a marker of the metabolic syndrome, these results may have clinical implications.

Dietary nutrition and energy balance have profound effects on adipose functions (6, 41) and can be manipulated in an experimental setting. For example, overfeeding causes a perturbation in energy balance and provides an opportunity to investigate the responses of adipokines and hormones and their potential roles in the development of obesity and diabetes (7, 12). This is the paradigm investigated by this study, because it is the first study, to our knowledge, to explore the nutritional regulation of visfatin in humans. The 7-d overfeeding protocol resulted in significant increases in body weight in all subjects which was determined to be a combination of %BF, %TF, and lean body mass. Our main finding was that the short-term overfeeding down-regulated the concentration of fasting serum visfatin. This reduction is significant in all participants and does not depend on the adiposity of the subjects.

This finding is consistent with previous research that confirms adipokines and other hormones are regulated by hormonal and nutritional factors such as overfeeding and exercise (20). For example, adiponectin expression in white adipose tissue was reduced by intragastric overfeeding in mice (42), whereas caloric restriction increases it and increases insulin sensitization in rats (43). Also, plasma ghrelin concentrations were reduced by 18% after 2 wk of overfeeding in healthy men (11). However, it is important to note that the reduction of visfatin in the present study does not appear to be linked to the increase in body fat, because no correlations were found between serum visfatin and %BF. This was true at baseline, as well as the changes after overfeeding. In addition, the reduction of visfatin was not correlated with the changes of IL-6 in our study, although IL-6 was shown to down-regulate visfatin gene expression in 3T3-L1 adipocytes in an in vitro experiment (2). TNF-α may also be a factor that mediates the reduction in visfatin, as obesity is associated with an increase in TNF-α concentrations (44). Intra-gastric overfeeding in mice resulted in an increase in plasma TNF-α concentrations in obese white adipose tissue (42). However, we did not measure serum TNF-α concentrations in the present study. Furthermore, many other adipokines not addressed in the present study may potentially influence the response of visfatin to a positive energy balance. There are 2–4 dozen cytokines secreted by adipocytes. The interplay between them and the effect on insulin resistance and lipid metabolism remain unclear at the current time. More studies are required to address these issues.

In summary, 61 young men participated in a 7-d overfeeding protocol. Visfatin concentrations at baseline and in response to the overfeeding did not correlate with the phenotypes of insulin resistance or body compositions in healthy young men. These results largely differ from those obtained from mice (1). Our data present new evidence that the regulation of visfatin at physiologic conditions in humans may differ from what has been observed in rodents, similar to the differences documented in resistin and TNF-α (9). We found that serum triacylglycerols are strongly correlated with fasting serum visfatin, and the correlation is independent of age and body fat. Moreover, short-term overfeeding resulted in a significant reduction of serum visfatin concentrations. Our results suggest that visfatin may play a role in lipid metabolism in healthy young men.

We thank all the volunteers for participating, Curtis French and Jennifer Shea for contributing to the data collection, and P Wang and V Gadag (Community Health, School of Medicine, Memorial University) for assisting with the statistical analysis.

GS was responsible for the study design, data analysis, and writing of the manuscript. JB assisted with the data collection, statistical analysis, and revision of the manuscript. SK contributed to the recruitment and overfeeding of volunteers and made some revisions. SV and VG provided excellent comments on the paper. DP and DF were responsible for the data collection. ER supervised the measurement of IL-6. Y-GX and HZ were involved in the data collection. GS holds the position of chair of pediatric genetics, which is supported by Novartis Pharmaceuticals. None of the other authors had a conflict of interest to disclose.

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