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INFLAMMATORY CYTOKINE IFNγ, IL-6, AND IL-10 ASSOCIATION WITH CHILDHOOD OBESITY

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*Childhood obesity carries a high risk of serious life-threatening cardiometabolic diseases in adulthood, which are associated with low-grade inflammation. The aim of the present study was to measure serum cytokine concentrations in obese children recruited during endocrinology consultations and compared to lean control the results. Blood serum concentrations of interferon gamma (IFNγ), IL-1β, Interleukin 6 IL-6, IL-10, and TNF-α were analysed applying Luminex xMap technology with Millipore reagent kits. Statistical analyses were performed using t-test comparisons and Spearman correlations. Obese children had highly significant increased levels of circulating IFNγ (*p *< 0.0001), IL-6 (*p *< 0.0001), and IL-10 (*p *< 0.0001), compared to lean controls. IL-1β and TNFα levels, however, were not elevated. Significant correlation of serum cytokines to per cent excess body mass was only observed with IL-6 (r_s = 0.21,* p *< 0.03), although IL-1β (r_s = 0.18,* p *< 0.08) results were suggestive of a trend. A significant association of obesity in childhood with serum concentrations of IFNγ, IL-6, and IL-10 is consistent with a role for low-grade inflammatory processes early in the aetiology of this disease. IL-6 further appears to be a candidate cytokine for assessment of degree of sub-acute inflammation associated with excess weight in the young.*

INTRODUCTION

The frequency of obesity in children throughout the world has increased rapidly in recent decades, creating serious health and social problems, resulting in a decreased quality of life in the near term as well as in subsequent reductions in life expectancy. Not only is obesity a primary disorder of energy-regulatory processes in the body, it is comorbid with a number of life-threatening cardio-metabolic diseases, the consequences of which already markedly increase the financial burden of health care for individuals and loom as major catastrophes for countries and society as a whole.

Although obesity can be characterised as an energy storage disorder, it is also associated with low-intensity inflammation, independent of the association between insulin resistance and sub-acute inflammation (Inadera, 2008; Singer and Lumeng, 2017; Mărginean *et al*. 2020). Many of the illnesses comorbid with obesity (e.g., osteoarthritis, skin disorders, asthma, even cognitive impairment) have an inflammatory component (Vendrell and Chacon, 2013; Krasteva *et al*., 2018; Stefanadi *et al*., 2018; Wang and He, 2018; Buie *et al*., 2019; Suhett *et al*., 2021), including type 2 diabetes mellitus (T2DM), dyslipidemia, atherosclerosis, and other cardiovascular diseases (CVD) (Herder *et al*., 2007; Yeste

et al., 2007; Carolan *et al*., 2014; Lund *et al*., 2020). The discovery of adipocytokines synthesised mainly by adipocytes further suggests an attractive mechanism for molecular signalling between obese adipose tissue and other organ systems. Moreover, obesity is directly related to increased inflammatory processes without evidence of concurrent active infection (Nguyen *et al*., 2009; Mărginean *et al*., 2020), consistent with the notion that sub-acute inflammation in the absence of frank infection may be an important mechanism through which disparate comorbid diseases are linked to obesity.

Several cytokines are associated with low-intensity inflammation in the context of obesity. Obese mice that are interferon gamma (IFNγ) deficient have significantly reduced expression of adipose tissue compared to lean controls; moreover, they have decreased accumulation of adipose tissue inflammatory cells and better glucose tolerance (Rocha *et al*., 2008). This leads to the understanding that IFNγ may be involved in the development of obesity. Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine. Its concentrations are elevated in obese children and adolescents (Gallistl *et al*., 2001), and it is involved in the development of obesity-associated insulin resistance (Bing, 2015). Interleukin 6 (IL-6) not only regulates inflammation and the acute phase response to tissue injury, but also circulating IL-6 levels are also positively correlated with adipose mass (Kern *et al*., 2001). Its levels decrease after weight loss (Marti *et al*., 2018). Interleukin-10 (IL-10) showed elevated level in type 2 diabetes mellitus patients compared to healthy controls (Al-Shukaili *et al*., 2013), but was not observed to be elevated in children with obesity compared to normal weight children (Glowinska and Urban, 2003). Finally, tumour necrosis factor (TNF-α), an adipocytokine involved in systemic and acute phase inflammation, is elevated in obesity and declines during reductions of body mass as insulin sensitivity increases (Hotamisligil *et al*. 1995). This finding is further supported by the observation that obese patients experiencing reductions in body weight by at least ten per cent using various methods have significant reductions of inflammation markers in comparison to their levels before the weight loss (Forsythe *et al*., 2008; Mart *et al*., 2018). Further, elevated TNF-α was associated with increased abdominal obesity (Beberashvili *et al*., 2019) in individuals with normal BMI, suggesting that TNF-α is increasing before BMI is evaluated as obese.

The aim of the present study was to investigate whether low-intensity inflammation (characterised by inflammatory cytokine IFNγ, IL-6, and IL-10) is an early characteristic of obesity, by measuring serum cytokine concentrations in children with a relatively brief history of obesity (lasting 1–4 years) and comparing the results to those of a non-obese control group.

MATERIAL AND METHODS

This case control study included children with obesity as the experimental group and adolescents with normal body mass as the control group. Obesity was established in accordance with WHO criteria defining body mass index (BMI, kg/m^2), calculated and applied to age-, height-, and gender-appropriate tables, to be at least at the 97^{th} percentile. Control group subjects were healthy adolescents, thereby excluding underweight or overweight volunteers.

A total of 102 obese children were selected from otherwise healthy patients referred by their family physicians to the Endocrinology Outpatient Clinic of the Children's Clinical University Hospital in Rīga, Latvia, with primary obesity as the presenting complaint. Exclusion criteria were any clinical indications of associated concurrent disease or disorder, including elevated C-reactive protein levels (C-reactive protein < 5 mg/l level was considered normal) and elevated HbA1c level (a 4–5.99% reference ranges of HbA1c level was considered normal). A total of 100 healthy normal-weight controls attending Jūrmala Health Care College volunteered as comparison group participants in this study, where exclusion criteria likewise included any clinical indication of disease or disorder.

The control group was selected from a population of normal-weight adolescents. This group, as non-obese children, were not "pre-obese".

The experimental protocol was approved by the Scientific Research Ethics Committee of the University of Latvia Institute of Experimental and Clinical Medicine, and written informed consent was obtained from study participants and their parent/legal guardian.

Anthropometric parameters were initially measured, and a venous blood sample was obtained. Serum was isolated for clinical laboratory determination of IFNγ, IL-1β, IL-6, IL-10, and TNF-α concentrations applying Luminex xMap technology with the Millipore MPXHCYTO-60K-06 MILLIPLEX MAP Human Cytokine/Chemokine Panel kit.

Data were statistically analysed using GraphPad Prism 5.01 and StatPlus : mac 5.4 data statistical analysis software. The arithmetic mean and standard deviation (SD) were calculated for all parameters, and a t-test assuming unequal variances was used to analyse differences in means between groups, with statistical significance for each comparison assumed at $p < 0.05$. To assess possible relationships between the severity of obesity and individual cytokine levels, Spearman correlation coefficients were calculated for each cytokine along with the *p*-value for each coefficient.

RESULTS

The children with obesity had a mean (± SD) age of 11.2 (± 3.3) years, mean weight of 66.6 (± 23.0) kg and BMI > 97^{th} percentile, according to WHO criteria of children obesity. The control group mean BMI was 21.20 (±0.20) kg/m^2.

Comparison of concentrations of IL-1β and of TNF-α in obese children to those of the normal-weight adolescents

Table 1. Correlation coefficient and significance level of each cytokine with per cent excess body mass in obese children

	Spearman correlation with % excess body mass	*p*-value of Spearman correlation
IFNγ	0.03	0.74
IL-1β	0.18	0.08
IL-6	0.21	0.03
IL-10	0.11	0.29
TNF-α	0.00	0.99

yielded no significant difference. However, very highly significant differences were observed comparing concentrations of the other cytokines tested. In every case, circulating levels of IFNγ, IL-6, and IL-10 were elevated ($p < 0.0001$) in obese children in comparison to their lean controls.

In addition, Spearman correlation analysis to determine possible association between the concentration of circulating cytokines and the amount of excess body mass in obese children (calculated as a percentage above ideal weight for that gender at that age and height), yielded a weak, though significant, correlation with IL-6 and a non-significant, though suggestive, relationship in the case of IL-1β (see Table 1).

DISCUSSION

It is firmly established that obesity in adulthood is directly associated with an elevation of inflammatory processes in the absence of concurrent infection (Nguyen *et al*. 2009; Saltiel and Olefsky, 2017; Karczewski *et al*., 2018; Fang *et al*., 2020). We investigated whether this association was as robust in children lacking an extended history of obesity.

The control group was selected from a population of normal-weight adolescents. These were, as non-obese children, not simply "pre-obese".

The present study affirmed and strengthened the association of increased serum IFNγ concentration with elevated body weight in children, as described previously (Utsal *et al*., 2012), revealing a very highly significant difference of IFNγ concentration in obese children when compared to lean adolescents. However, there was clearly no correlation between INFγ concentration and per cent excess body mass among the obese children, indicating that IFNγ, at least at this stage or duration of obesity, is not reflective of relative adipose tissue mass. Possibly, a weight or time criterion in the aetiology of adiposity had not been reached to culminate in IFNγ production and release. Recent studies showed that IFNγ levels were significantly higher in individuals with type 2 diabetes mellitus compared to healthy controls (Amin *et al*., 2019; Hasan *et al*., 2019). It is well known that childhood obesity is a risk factor for adult type 2 diabetes mellitus (Fang *et al*., 2019). Alternatively, there may not have been a large enough range of excess weights or of IFNγ concentrations in the obese group to statistically establish significance of a correlation.

Concentration of IL-1β in our study did not show significant association, although in a study with severely obese school children, IL-1β, IL-6, and TNF-α levels were significantly higher in severely obese children with metabolic syndrome, compared to a normal body weight group (Al-Shorman *et al*., 2017), IL-1β is associated with low-intensity inflammation, although we did not observe this.

Previous reports of rapidly decreasing IL-6 levels in children and adolescents experiencing weight loss point to an important association between this cytokine and excess adiposity, with serum IL-6 levels correlated with changes in BMI due to food intake restriction combined with physical activity (Gallistl *et al*., 2001). Moreover, obese patients undergoing bariatric surgery showed significantly decreased IL-6 levels following surgical intervention and weight loss, with IL-6 concentrations strongly correlated with BMI (Illan-Gomez *et al*., 2012). In addition, positive correlations between plasma IL-6 and obesity and glucose intolerance have been observed in both adolescents and children (Kern *et al*., 2001) Consistent with those results, the present study confirmed a very highly significant increase in circulating IL-6 in obese children in comparison to lean controls. Furthermore, our observed correlation between IL-6 level and per cent excess body mass in children was comparable to that previously found between IL-6 and BMI changes (Gallistl *et al*., 2001). Although this correlation admittedly is weak, it nevertheless indicates a relationship between this cytokine and obesity in childhood that needs to be explored further to fully understand the molecular mechanisms linking low-grade inflammation and adiposity.

We observed very significantly elevated IL-10 levels in obese children in comparison to non-obese controls. In a previous study, the IL-10 level was elevated in obese women, but low IL-10 levels were observed in women with metabolic syndrome (Esposito *et al*., 2003). Recent studies showed elevated IL-10 levels not only in obese individuals, but also in individuals who had developed complications like osteoarthritis, strengthening the IL-10 cytokine role in obesity (Schwarz *et al*., 2018; Silawal *et al*., 2019).

Contrary to previous studies demonstrating elevated TNF-α levels in obese children (Rocha *et al*., 2008) we did not observe this result. One explanation could be that obese children were not uniform in terms of duration and/or severity of obesity, and that this heterogeneity in adipose tissue might result in lack of a clear signal by the adipocytokine TNF-α. It should also be noted that the large variability in some of the cytokine concentrations could also be the result of different obesity stages and durations in the case group. A recent study reported TNF-α and IL-6 involvement in liver and colorectal cancer development (Kern *et al*., 2018), indicating the importance and involvement of the inflammatory cytokine in neoplastic processes.

Previous studies in adults have supported a role for cytokines in providing a link between obesity and other pathological conditions that are often comorbid with obesity (Vendrell and Chacon, 2013). The elevation of specific cytokines

in childhood obesity in the present study, where the duration of the disorder is much shorter, is consistent with a causative or facilitative role of adipocytokines in promoting other subsequent comorbidities. Most importantly, a recent study investigating the association of fat deposition and systemic low-grade inflammation in peripubertal girls confirmed that fat deposition contributes to inflammation, but not vice versa (Wen *et al*., 2014). Moreover, the term "low-intensity" may well be a misnomer, as there is now strong evidence that obesity in childhood triggers a range of inflammatory responses, from increased concentrations of immune cells to accelerated metabolic gene expression — precursors to metabolic disease in adulthood, especially T2DM and CVD (Carolan *et al*., 2013).

CONCLUSIONS

Markedly elevated levels of IFNγ, IL-6, and IL-10 in obese children indicate the presence of substantial low-intensity inflammatory processes early in the aetiology of this disorder. Contrary to expectations, only IL-6 concentrations are significantly, albeit weakly, correlated with adiposity in children. Further studies should be performed to estimate inflammation of childhood obesity.

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The authors declare no conflict of interest.

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IEKAISUMA CITOKĪNU IFNγ, IL-6 UN IL-10 SAISTĪBA AR APTAUKOŠANOS BĒRNIEM

Aptaukošanās bērnu vecumā ir paaugstināts risks kardiometabolām slimībām, kuras saistītas ar zema līmeņa iekaisumu pieaugušo vecumā. Šī pētījuma mērķis ir noteikt seruma citokīnu koncentrāciju bērniem ar aptaukošanos, kuri tika izvēlēti bērnu endokrinologa konsultācijas laikā, iegūtie rezultāti tika salīdzināti ar normāla svara kontroles grupas rezultātiem. IFNγ, IL-1β, IL-6, IL-10 un TNF-α asins seruma koncentrācijas tika noteiktas, izmantojot Luminex xMap tehnoloģiju un Millipore reaģentu komplektu. Statistikas aprēķini tika veikti, izmantojot t testu un Sperman korelācijas. Bērniem ar aptaukošanos ir statistiski ticami augstāka IFNγ ($p < 0.0001$), IL-6 ($p < 0.0001$) un IL-10 ($p < 0.0001$) koncentrācija serumā, salīdzinot ar normāla svara kontroles grupu. Savukārt IL-1β un TNF-α koncentrācija serumā nebija paaugstināta. Statistiski ticama seruma citokīnu korelācija procentuālai ķermeņa masa tika novērota IL-6 ($r_s = 0.21$, $p < 0.03$), tomēr IL-1β ($r_s = 0.18$, $p < 0.08$) iegūtais rezultāts būtu jāpēta tālāk. Statistiski ticamai saistībai starp bērnu aptaukošanās seruma koncentrāciju un IFNγ, IL-6 un IL-10 ir nozīmīga loma agrīna zema līmeņa iekaisuma aptaukošanās etioloģijā. IL-6 turpmāk būtu jāpēta, lai izvērtētu subakūtu iekaisuma saistību bērniem ar palielinātu svaru.