Low-grade systemic inflammation and the risk of type 2 diabetes in obese children and adolescents

Anhelli Syrenicz [1], Barbara Garanty-Bogacka [2], Małgorzata Syrenicz [2], Aneta Gębala [2], Mieczysław Walczak [3]

[1] Department of Endocrinology, Arterial Hypertension and Metabolic Diseases, Pomeranian Medical University, Szczecin, Poland
[2] Independent Laboratory of Children's Diseases, Pomeranian Medical University, Szczecin, Poland
[3] 2nd Department of Children's Diseases, Pomeranian Medical University, Szczecin, Poland

Correspondence to: Anhelli Syrenicz
Department of Endocrinology, Arterial Hypertension, and Metabolic Diseases, Pomeranian Medical University
4 Arkońska Street, 71-455 Szczecin, POLAND
PHONE: +48 91 4316241; FAX: +48 91 4316243
EMAIL: anhelli@asymed.ifg.pl

Submitted: July 1, 2006 *Accepted: July 17, 2006*

Key words: **inflammation; obesity; type 2 diabetes; children**

Neuroendocrinol Lett 2006; **27**(4):453–458 **PMID:** 16892000 NEL270406A18

Abstract

BACKGROUND: There is growing evidence that low-grade systemic inflammation is closely involved in the pathogenesis of type 2 diabetes.
OBJECTIVE: The aim of this study was to investigate the relationship between serum inflammatory markers and selected parameters known as risk factors of type 2 diabetes in obese children and adolescents.
SUBJECTS AND METHODS: Fasting levels of C-reactive protein (CRP), fibrinogen (FB) interleukin-6 (IL-6), interleukin 1-β (IL-1β), glucose, insulin, total, HDL and LDL cholesterol, triglycerides, white blood cell count (WBC) and fasting glucose to insulin ratio (FGIR) were measured in 281 obese children and adolescents. Pearson's correlation was used for assessing the relationship between inflammatory markers and selected clinical parameters.
RESULTS: Inflammatory markers correlated significantly with insulin resistance indices, HbA1c, lipid profile, hypertension, positive family history of type 2 diabetes, low physical fitness, and mixed high-fat and high-carbohydrate diet.
CONCLUSIONS: Serum inflammatory markers were significantly correlated with most factors implicated in the development of type 2 diabetes. These data provide additional support for previously reported in adults relationship between subclinical inflammation and the risk of type 2 diabetes.

Introduction

The link between obesity and the increased risk of developing insulin resistance, type 2 diabetes and cardiovascular disease have still not been fully elucidated [3, 8, 18, 20, 24]. During the last decade it has become increasingly clear that the adipose tissue itself produces and releases a number of cytokines and hormone-like proteins such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), leptin and adiponectin, all of which may be of importance for the association between obesity and health complications [10,17,24, 28,31,37]. There is increasing evidence that cytokine-induced acute-phase response, sometimes called low-grade inflamma-

ORIGINAL ARTICLE

tion is closely involved in the pathogenesis of type 2 diabetes and its vascular complication such as accelerated atherosclerosis [6,31]. Interleukin-6 is a major cytokine which stimulate the production of acute-phase proteins such as C-reactive protein (CRP) and fibrinogen (FB) [13]. Elevated levels of IL-6 has been shown to increase the risk of type 2 diabetes [32,37]. However, in addition to IL-6, other cytokines, such as IL-1β or TNF-α are central mediators of inflammatory reaction. It is well known that cytokines act as a network in stimulating the production of acute-phase proteins. It has been shown that the effect of IL-6 on CRP synthesis largely depend on an interaction between IL-6 and IL-1β [13]. Elevated levels of CRP are known to predict the development of type 2 diabetes [21,32] and cardiovascular disease [6,35].

Obesity in children is clinically worrisome because it is usually associated with low physical activity and poor diet which may lead to increased risk of metabolic or cardiovascular diseases later in life [21,23,34,40]. The mechanisms that link inflammatory markers with pathologic processes of insulin resistance and hyperlipidemia are poorly understood in children [26,41]. Therefore, the aim of this study was to investigate the relationship between serum markers of inflammation and selected anthropometric and clinical parameters known as traditional risk factors for type 2 diabetes.

Material and methods

Patients

The study group comprised 281 obese children (151 boys and 130 girls), aged 5.5–18y. Obesity was recognized on the basis of body mass index (BMI) greater than 97th percentile for age and gender [29]. None of the children had any acute or chronic infections, cancers, autoimmunological diseases, hormonal abnormalities as well as hepatic or renal dysfunction. All children were in good health and taking no medications, alcohol or tobacco.

Physical examination, body weight, height, waist and hip circumferences were performed while the patients were fasting and wearing only undergarments. Mean systolic and diastolic blood pressure values were obtained from 24-hour ambulatory blood pressure monitoring. Hypertension was recognized on the basis of this procedure, according to references values for age and gender.

Detailed individual and family history were obtained from the personal interview with the parents. A positive family history of type 2 diabetes (DM 2) was determined by parent's report of diabetes in a first-degree relative. Twenty-four-hour nutrient intakes were calculated with food-composition tables and patients' weekly diet diaries. All subjects or their parents were asked to complete a 3-day food intake record and record leisure-time physical activity to assess dietary adherence and physical activity. Diet was classified as high-fat (Diet F) if fat content exceeded 30% of total daily energy, high-sugar (Diet S) if sugar constituted most of carbohydrate intake or mixed (Diet M) when child's diet contained the meals rich in both fat and sugar. Regular strenuous physical fitness less than 1 hour per week was categorized as low physical activity.

The study was approved by the Ethical Committee of the Pomeranian Medical University and informed consent as well as assent was obtained.

Assessment of body adiposity

Standard, electronic scale and stadiometer were used to determine weight and height, respectively. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Since BMI changes with age, the BMI-SD score was also calculated. The minimal abdominal circumference between the xiphoid process and the iliac crest was measured to define waist circumference. The hip circumference was measured at the widest part of the gluteal region. Waist-to-hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. Measurement of body composition was performed by means of bioelectrical impedance (Bioelectrical Impedance Analyzer Tanita 131, Japan) with an applied current of 0.8 mA at a fixed frequency of 50 kHz.

Assessment of pubertal development

The standard clinical five-stage scale described by Tanner and Marshall was applied to assess pubertal development of the subjects.

Serum measurements

Blood samples were obtained in the morning after an overnight fast. Circulating IL-6 and IL-1β levels were determined by ELISA with the use of the Quantikine high-sensitivity kit (R & D Systems, Minneapolis, MN, USA). CRP was measured by immunoturbidimetric, high-sensitivity method (CRP-Latex, Olympus), fibrinogen (FB) – by coagulometric method according to Clauss. Serum glucose levels were measured by an enzymatic colorimetric assay using a modified glucose oxidase-peroxidase method and a Glucose HK analyzer (Olympus) and free insulin concentrations were determined by double-antibody RIA (Pharmacia RIA kit). Total cholesterol (T chol) and triglyceride (TG) levels were measured in serum by automated enzymatic procedures (Olympus). LDL cholesterol (LDL chol) was measured after separating LDL-fraction from fresh fasting sera by sequencial ultracentrifugation. HDL cholesterol (HDL chol) was determined automatically by routine laboratory test (HDL cholesterol, Olympus).

Fasting insulin as well as fasting glucose to insulin ratio (FGIR) were chosen as a surrogate markers of insulin resistance [14,32].

TABLE 1. Clinical characteristics of the study subjects

Variable	Mean ± SD		
	male	female	p
Age (y)	12.5 ± 2.7		
BMI (kg/m^2)	28.2 ± 3.7	29.0 ± 4.0	< 0.05
BMI-SD	3.2 ± 1.2	3.7 ± 1.4	< 0.05
% fat	31.4 ± 6.8	36.5 ± 5.0	< 0.01
Fat mass (kg)	22.3 ± 8.3	26.3 ± 9.4	< 0.05
Waist circumference (cm)	96.4 ± 11.9	93.6 ± 10.5	< 0.05
WHR	0.99 ± 0.05	0.93 ± 0.07	< 0.05
Birthweight (kg)	3.4 ± 0.6	3.3 ± 0.6	
Systolic blood pressure -SBP (mm Hg)	113.1 ± 10.7		
Diastolic blood pressure - DBP (mm Hg)	63.8 ± 8.2		
Obesity duration (y)	6.7 ± 3.1		
	n (%)		
Pubertal stage 1	80 (28.5)		
Pubertal stage 2-5	201 (71.5)		
Hypertension	50 (17.8)		
Acanthosis nigricans	103 (36.7)		
Diet F	59 (21.1)		
Diet S	67 (23.8)		
Diet M	155 (55.1)		
Low physical activity	189 (67.3)		
Positive family history of DM 2	94 (33.5)		

TABLE 2. Biochemical characteristics of studied children

Parameter	Mean ± SD / * Median (Q25% – Q 75%)
Glucose (mmol/L)	4.89 ± 0.6
Insulin (pmol/L)*	106.4 (77.5 – 162.2)
FGIR*	5.9 (4.0 – 8.0)
HbA1c (%)	5.5 ± 0.4
T chol (mg/dL)	185 ± 36.9
HDL chol (mg/dL)	50.6 ± 12.2
LDL chol (mg/dL)	108.2 ± 32.7
TG (mg/dL)*	104.5 (76.9 – 149.3)
CRP (mg/dL)	1.1 ± 0.9
FB (mg/dL)	320.5 ± 61.2
IL-6 (pg/mL)*	1.5 (0.9 – 2.2)
IL-1β (pg/mL)	0.4 (0.2 – 0.7)
WBC (G/L)	7.4 ± 2.1

Statistical analysis

All statistical analyses were performed with the version 9.0 of the SPSS for Windows software (SPSS Inc., Chicago, Ill., USA). All values were expressed as means ± standard deviation (SD) or median with lowest (Q 25) and higher quartile (Q 75). Comparisons between two groups were tested with Mann-Whitney U-test. Parameters with skewed distributions were log-transformed before analysis. Association of biochemical and clinical characteristics were examined by Pearson's correlation. A p-value less than 0.05 was considered statistically significant.

Results

Table 1 demonstrated the relevant anthropometric and clinical variables in the study population.

There were significant differences between girls and boys in body adiposity and body fat distribution. Percent body fat and fat mass were higher in girls, whereas waist circumference and WHR were significantly higher in boys. Studied boys had also higher mean birthweight although the difference did not reach statistical significance.

Among studied subjects approximately one third were prepubertal and two third were pubertal or postpubertal. One third of participants had clinical signs of acanthosis nigricans (AN) which has been argued to indicate insulin resistance state [14].

Values of selected biochemical parameters are presented in Table 2.

Fasting insulin was significantly higher in girls than in boys (median insulin 119.8 pmol/L in girls vs. 98.5 pmol/L in boys; $p<0.05$) and FGIR was significantly higher in boys (median FGIR 6.4 in boys vs. 5.3 in girls; $p<0.01$). Lipid levels were comparable in both genders, except TG level which was higher in boys. Fibrinogen level was significantly higher in girls than in boys (mean FB 336.7 mg/dL in girls vs. 306.5 mg/dL in boys, $p<0.05$). HbA1c, CRP, IL-6, IL-1β and WBC were comparable in both genders.

Pearson's correlation coefficients between inflammatory markers and selected clinical parameters are presented in Table 3.

All inflammatory markers were positively correlated with adiposity and abdominal obesity, blood pressure, acanthosis nigricans, low physical fitness, and positive family history of type 2 diabetes. The highest correlation's coefficient values were found between "mixed" diet and markers of inflammation.

The next analyses were performed after adjustment for age, sex, BMI, and fat mass to avoid the influence of these variables. Correlation between inflammatory markers and selected biochemical parameters are demonstrated in Table 4.

After adjustment for age, sex, BMI and fat mass, the correlation with indices of insulin resistance remained significant for CRP, fibrinogen and white blood cell count (Table 4). There was a trend for association between fasting insulin and IL-6 ($r = 0.13$, $p = 0.055$) as well as between FGIR and IL-6 ($r = 0.13$, $p = 0.055$). HDL cholesterol correlated inversely with FB and IL-6, and triglycerides correlated positively with all inflammatory markers when controlling for age, sex, BMI, and fat mass. Overall, these findings suggest that in obese children chronic inflammation is associated with

lipid profile characteristic for type 2 diabetes.

Discussion

To the best of our knowledge, this study is the first to investigate the relationship between serum inflammatory markers and risk factors of diabetes mellitus type 2 in relatively large sample of obese children and adolescents. There has been a recent explosion of studies suggesting that low-grade systemic inflammation and activation of the innate immune system are closely involved in the pathogenesis of type 2 diabetes [8,31, 33,37,44].

In our study the significant correlation of serum inflammatory markers with adiposity and body fat distribution was found. The association between low-grade inflammation and BMI has previously been reported among obese adults [45] and children [26,41]. It is not unexpected because adipose tissue is a main source of plasma IL-6: as much as 30% of circulating IL-6 originates in adipose tissue [22]. Moreover, cells deriving from omental as opposed to subcutaneous fat secrete 2 to 3 times more IL-6 in vitro [12]. Elevated concentrations of acute phase inflammatory reactants in plasma were previously found in obese adults and children, suggesting that obesity itself is a state of chronic, subclinical inflammation [4,7,9,15,17,39].

Although it is well established that insulin resistance and impaired insulin secretion are central to the pathogenesis of type 2 diabetes, it is still unclear how these abnormalities arise and how they related to the many different risk factors as well as clinical and biochemical features common in type 2 diabetes, such as abdominal obesity, hypertension and dyslipidemia. Our data suggest a possible link between inflammatory markers and insulin resistance. For practical reason, we used fasting insulin level and fasting glucose to insulin ratio (FGIR) as a surrogate markers of insulin resistance. Both of these indices well correlated with more direct measures of insulin resistance [14,32]. In our study, significant correlation between serum markers of inflammation and insulin resistance remained, although weaker, after adjustment for age, sex, BMI and fat mass. Moreover, a strong correlation between inflammatory indices and acanthosis nigricans – a cutaneous marker of insulin resistance was found. Mechanism by which proinflammatory cytokines such as IL-6 and TNF-α can cause insulin resistance is still unclear. Experimental studies has shown that chronic exposure to human recombinant IL-6 resulted in impairment of early insulin receptor signaling in the liver of mice [19]. Chronic infusion of IL-6 also reduced hepatic insulin receptor autophosphorylation by 60% and tyrosine phosphorylation of insulin receptor substrates-1 and -2 by 60% and 40%, respectively. Inflammatory cytokines such as IL-1β and IL-6 also downregulate PPAR-γ expression [38].

Genetic and environmental factors are generally considered to be responsible for type 2 diabetes, and among these environmental factors, the high-fat level and overly refined foods in the typical western-style diet are considered to be two of the major causes of obesity and associated insulin resistance. It has been suggested that high-fat diet can reduce the number of

TABLE 3. Pearson's correlation between inflammatory markers and clinical parameters

	CRP	FB	IL–6	IL–1β	WBC
	r	r	r	r	r
Age	0.06	0.03	–0.09	–0.08	–0.09
Sex	0.03	0.25***	0.03	0.01	0.10
Pubertal stage	0.01	0.09	–0.10	–0.07	–0.10
BMI	0.10	0.24**	0.21**	0.22 *	0.12
BMI–SD	0.16*	0.26***	0.26***	0.30 ***	0.17*
% fat	0.24***	0.38***	0.31***	0.21*	0.23***
Fat mass	0.15*	0.29***	0.24***	0.21*	0.16*
Waist	0.07	0.15*	0.15	0.19	0.09
WHR	0.15*	0.05	0.16*	0.20*	0.17*
SBP	0.23**	0.20*	0.35***	0.19	0.23**
DBP	0.17*	0.08	0.16	0.10	0.17*
Hypertension	0.26***	0.23**	0.32***	0.12	0.25***
AN	0.25***	0.25***	0.36***	0.37***	0.24***
Diet F	0.18**	0.14*	0.19**	0.02	0.17*
Diet S	0.18**	0.07	0.19**	0.16	0.19**
Diet M	0.28***	0.16**	0.30***	0.15	0.26***
Low ph. act.	0.23***	0.21***	0.25***	0.24**	0.24***
Birthweight	–0.06	–0.07	–0.04	–0.07	–0.08
Family history of DM 2	0.14*	0.13*	0.19**	0.21*	0.18**

All inflammatory markers were log-transformed for statistical analyses.
* 0.01<p<0.05 ** 0.01<p<0.01 *** p<0.001.

TABLE 4. Correlation's coefficients between inflammatory markers and biochemical parameters

	CRP	FB	IL–6	IL–1β	WBC
	r	r	r	r	r
Fasting glucose	0.14*	0.08	0.09	0.08	0.15*
Fasting insulin	0.18**	0.14*	0.13	0.09	0.19**
FGIR	0.17**	0.13	0.13	0.12	0.18**
HbA1c	0.18**	0.15*	0.28***	0.13	0.17**
T Chol	0.20**	0.16**	0.14*	0.19*	0.21**
LDL chol	0.21**	0.15*	0.16*	0.16	0.20**
HDL chol	–0.03	–0.22***	–0.14*	–0.11	–0.10
TG	0.17**	0.21**	0.25***	0.15*	0.21**

All inflammatory markers were log-transformed for statistical analysis.
* 0.01<p<0.05 ** 0.01<p<0.01 *** p<0.001.

insulin receptors and decrease the activity of the glucose transport system and the intercellular metabolism of glucose [16]. Moreover, high-fat and hypercaloric diets are known to stimulate the release of cholecystokinin and to cause pancreatic enlargement. On the other hand, rats fed on a high-fructose diet can develop a cluster of abnormalities, such as hyperinsulinemia, glucose intolerance and hypertension. In addition, a high-fructose diet may cause the inhibition of glucose-6-phosphatase and impair the hepatic carbohydrate metabolism, which leads to insulin resistance [16]. In the study by Huang and co-workers [16] it was found that both high-fat and high-fructose diet led to glucose intolerance in rats. However, whereas high-fructose diet caused hyperinsulinemia, high-fat diet resulted in impaired pancreatic function of insulin secretion and glucose intolerance.

It has been recently shown that many dietary factors may contribute to activation of innate immunity in the genetically or metabolically programmed individual [27,42]. Meal intake increases adipose tissue IL-6 production by some fivefold when measured by subcutaneous microperfusion [27]. There is also evidence that glucose intake induces acute oxidative stress and inflammation at the cellular and molecular level for a period of three hours, and a mixed fast-food meal causes similar responses for next four hours [7]. The most important factors leading to activation of immune system seem to be advanced glycation end products (AGEs). Although AGEs are best known as endogenous products of glycation of body proteins in diabetes, they are also present in food as a result of heat-generated reactions between sugars and proteins or lipids. Vlassara et al. [42] showed that administration of a high-AGE diet to diabetic subjects caused increasing of serum CRP concentrations. In the present study we found the significant correlation between serum inflammatory markers and type of the diet. The strongest correlation was found between "mixed" high-fat and high-sugar diet and acute phase proteins and proinflammatory cytokines. It may indicate that nutrient-induced low-grade inflammation may occur relatively early in life.

Our results also confirm that low physical activity may contribute to the activation of innate immunity. This is supported by previous studies showing positive relationship between physical activity and circulating acute-phase reactants [1]. Lack of physical activity is well-known risk factor for developing of type 2 diabetes [5]. Exercises improve insulin resistance in large part by altering glucose transporters [36], but study by Nemet et al. [26] had suggested that potentially beneficial effects of exercise in obese children may be diminished in the absence of accompanying decreases in fat mass. In the contrary to our findings, the others [25,26] found that an intense exercise in non-obese children caused significantly increase of inflammatory cytokines. Different methodology could explain dissimilar results. Classification of physical activity in our study was based on personal interview with parents and children, whereas Nemet et al. [25,26] used the direct measurements of oxygen consumption.

In the short-term, innate immunity has survival value and restores body homeostasis after an environmental threats such as microbial infection and physical or metabolic injury. However, in type 2 diabetes, it may be that prolonged lifestyle or environmental stimulants cause maladaptation to the normal physiological responses to stress, causing disease instead of restoration. A genetic or inborn propensity to a hyperresponsive innate immune system might be present in certain individuals. This hypothesis is supported by recent data showing that low birth weight (LBW) or disproportionate size at birth is associated with elevated levels of acute-phase reactants such as cortisol and fibrinogen in adult life [2,11,30]. We did not find significant correlation between serum inflammatory markers and birthweight in our patients. However, in our study the percent of children born with LBW was relatively small. Further investigations are needed to establish the reliable influence of LBW on activation of immune system.

In the present study the significant relationship between serum inflammatory markers and positive family history of type 2 diabetes was also found. Genetic predisposition is well-known risk factor for developing of type 2 diabetes. Recently, this genetic background was supported in the study by Vozarova et al. [43], who found that the C-174-G promoter polymorphism of the IL-6 gene is associated with type 2 diabetes both in native Americans and Caucasians. In our study, the genetic analysis was not performed so we could not state if mentioned above relationship was actually caused by this polymorphism.

In conclusion, our results indicate that previously reported association between low-grade systemic inflammation and the risk of type 2 diabetes may exist relatively early in life. From a clinical perspective, measurement of inflammatory markers may become a part of the standard evaluation of obese child and help to manage those overweight children who may be at high risk for the development of type 2 diabetes.

REFERENCES

1 Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch Intern Med 2002; **162**:1286–1292.
2 Barker DJ. Fetal origins of coronary heart disease. BMJ 1995; **311**:171–174.
3 Blaschke F, Takata Y, Caglayan E, Law RE, Hsueh WA. Obesity, peroxisome proliferator-activated receptor, and atherosclerosis in type 2 diabetes. Arterioscler Thromb Vasc Biol 2006; **26**:28-40.
4 Bruun JM, Verdich C, Toubro S, Astrup A, Richelsen B. Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alfa. Effect of weight loss in obese men. Eur J Endocrinol 2003; **148**:535–542.

5 Caballero AE. Metabolic and vascular abnormalities in subjects at risk for type 2 diabetes: the early start of a dangerous situation. Arch Med Res 2005; **36**:241-249.
6 Cummings DM, King DE, Mainous AG, Geesey ME. Combining serum biomarkers: the association of C-reactive protein, insulin sensitivity, and homocysteine with cardiovascular disease history in the general US population. Eur J Cardiovasc Prev Rehabil 2006; **13:**180-185.
7 Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 2004; **25**:4–7.
8 Duncan BB, Schmidt MI. The epidemiology of low-grade chronic systemic inflammation and type 2 diabetes. Diabetes Technol Ther 2006; **8**:7-17.
9 Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D. Effects of weight loss and lifestyle changes on vascular inflammatory markers in obese women. JAMA 2003; **289**:1799–1804.
10 Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. Diabetologia 2003; **46**:1594–1603.
11 Fernandez-Twinn DS, Ozanne SE. Mechanisms by which poor early growth programs type-2 diabetes, obesity and the metabolic syndrome. Physiol Behav 2006; **88**:234-243.
12 Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998; **83**:847–850.
13 Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Eng J Med 1999; **340**:448–454.
14 Galli-Tsinopoulou A, Karamouzis M, Nousia-Arvanitakis S. Insulin resistance and hyperinsulinemia in prepubertal obese children. J Pediatr Endocrinol & Metab 2003; **16**:555–560.
15 Glowinska B, Urban M. Selected cytokines (IL-6, IL-8, IL-10, MCP-1, TNF-alfa) in children and adolescents with traditional atherosclerosis risk factors: obesity, hypertension, diabetes mellitus. Wiad Lek 2003; **56**:109–116.
16 Huang B-W, Chiang M-T, Yao H-T, Chiang W. The effect of high-fat and high-fructose diets on glucose tolerance and plasma lipid and leptin in rats. Diabetes Obes Metab 2004; **6**:120–126.
17 Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. Am J Med Sci 2005; **330**:280.
18 Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000; **106**:473–481.
19 Klover PJ, Zimmers TA, Koniaris LG, Mooney RA. Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice. Diabetes 2003; **52**:2784–2789.
20 Kopelman PG. Obesity as a medical problem. Nature 2000; **404**:635–643.
21 Meigs JB, O'donnell CJ, Tofler GH, Benjamin EJ, Fox CS, Lipinska I et al. Hemostatic markers of endothelial dysfunction and risk of incident type 2 diabetes: the Framingham Offspring Study. Diabetes 2006; **55**:530-537.
22 Mohamed-Ali V, Goodrick S, Rawesh A, Kath DR, Miles JM, Yudkin JS, Klein S, Coppack SW. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alfa, in vivo. J Clin Endocrinol Metab 1997; **82**:4196–4200.
23 Mossberg HO. 40-year follow-up of overweight children. Lancet 1989; **2**:491–493.
24 Natali A, Toschi E, Baldeweg S, Ciociaro D, favilla S, Sacca L, Ferrannini E. Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. Diabetes 2006; **55**:1133-1140.
25 Nemet D, Oh Y, Kim H-S, Hill MA, Cooper DM. Effect of intense exercise on inflammatory cytokines and growth mediators in adolescent boys. Pediatrics 2002; **110**:681–689.
26 Nemet D, Wang P, Funahashi T, Matsuzawa Y, Tanaka S, Engelman L, Cooper DM. Adipocytokines, body composition, and fitness in children. Pediatr Res 2003; **53**:148–152.
27 Orban Z, Remaley AT, Sampson M, Trajanoski Z, Chrousas GP. The differential effect of food intake and beta-adrenergic stimulation on adipose-derived hormones and cytokines in man. J Clin Endocrinol Metabol 1999; **84**:2126–2133.
28 Ouch N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 2003; **14**:561–566.
29 Palczewska I, Niedźwiecka Z. Somatic development indices in children and youth of Warsaw. Developmental Period Medicine 2001; **2** (suppl. 1):113–114.
30 Philips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, Barker DJ. Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. Hypertension 2000; **35**:1301–1306.
31 Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004; **27**:813–823.
32 Pradhan AD, Cook NR, Buring JE, Manson JE, Ridker PM. C-reactive protein is independently associated with fasting insulin in nondiabetic women. Arterioscler Thromb Vasc Biol 2003; **23**:650–655.
33 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin-6, and the risk of developing type 2 diabetes mellitus. JAMA 2001; **286**:327–334.
34 Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. Metabolism 2006; **55**:113-118.
35 Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; **103**:1813–1818.
36 Schmitz KH, Jacobs DR Jr, Hong C-P, Steinberger J, Moran A, Sinaiko AR. Association of physical activity with insulin sensitivity in children. Int J Obes 2002; **26**:1310–1316.
37 Spranger J, Kroke A, Mohlig M, Hoffman K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes. Results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC) – Potsdam Study. Diabetes 2003; **52**:812–817.
38 Tanaka T, Itoh H, Doi K, Fukunaga K, Shintani M, Yamashita J, Chun TH, Inoue M, Masatsugu K, Sawada N, Saito T, Nishimura H, Yoshimasa Y, Nakao K. Down regulation of peroxisome proliferators-activated receptor gamma expression by inflammatory cytokines and its reversal by tiazolidinediones. Diabetologia 1999; **42**:702–710.
39 Weisberg SP, McCann D, Deasi M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; **112**:1796–1808.
40 Weiss R, Caprio S. The metabolic consequences of childhood obesity. Best Pract Res Clin Endocrinol Metab 2005; **19**:405-419.
41 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low-grade systemic inflammation in overweight children. Pediatrics 2001; **107**:1–6.
42 Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, Peppa M, Rayfield EJ. Inflammatory mediators are induced by dietary glucotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci USA 2002; **99**:15596–15601.
43 Vozarova B, Fernandez-Real J-M, Knowler WC, Gallart L, Hanson RL, Gruber JD, Ricard W, Vendrell J, Richart C, Tataranni PA, Wolford JK. The interleukin-6 (-174) G/C promoter polymorphism is associated with type-2 diabetes mellitus in Native Americans and Caucasians. Hum Genet 2003; **112**:409–413.
44 Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002; **51**:455–461.
45 Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: association with obesity, insulin resistance, and endothelial dysfunction. Arterioscler Thromb Vasc Biol 1999; **19**:972–978.