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SCIENCE DIRECT

Metabolism Clinical and Experimental 54 (2005) 1155–1161

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

High-sensitive C-reactive protein, tumor necrosis factor α, and cardiovascular risk factors before and after weight loss in obese children

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Received 17 November 2004; accepted 10 March 2005

Abstract

To confirm the existence of obesity-induced inflammation and to clarify the association between such inflammation and other cardiovascular risk factors, we investigated the relationships between high-sensitive C-reactive protein (hsCRP), tumor necrosis factor α (TNF-α), obesity, blood pressure, lipids, and insulin resistance in a long-term follow-up of obese children. We compared the serum concentrations of hsCRP, TNF-α, high-density lipoprotein cholesterol, and triglycerides as well as blood pressure and the insulin resistance index (homeostasis model assessment [HOMA]) of 14 nonobese and 31 obese children. Furthermore, we studied the changes in these parameters in 16 obese children who lost weight and in 15 obese children without weight change over a 1-year period. In the obese children, blood pressure ($P = .003$), HOMA ($P = .034$), and triglyceride ($P = .011$), TNF-α ($P = .015$), and hsCRP ($P < .001$) levels were significantly higher, whereas high-density lipoprotein cholesterol concentrations were significantly ($P = .015$) lower compared with the nonobese children. Weight loss was associated with a significant decrease in hsCRP ($P = .008$) and triglyceride ($P = .048$) levels, HOMA ($P < .001$), and blood pressure ($P = .019$), whereas there were no significant changes in the children with stable weight status. The changes in hsCRP and TNF-α levels over the 1-year period were not significantly correlated to the changes in lipids, blood pressure, and HOMA. Obese children demonstrated significantly higher levels of hsCRP and TNF-α compared with nonobese children. The chronic inflammation markers TNF-α and hsCRP were independent of lipids, blood pressure, and insulin resistance index. Weight loss was associated with the significant decrease of hsCRP and triglyceride levels, and blood pressure.

1. Introduction

Cardiovascular morbidity and mortality of obesity is associated with cardiovascular risk factors such as dyslipidemia (hypertriglyceridemia and low high-density lipoprotein cholesterol [HDL-C]), hypertension, and impaired glucose metabolism (metabolic syndrome), leading to atherosclerosis [1,2]. These clinical features already occur in childhood obesity [3-5]. Recently, further markers of atherosclerosis have been found, such as the inflammation factors high-sensitive C-reactive protein (CRP) (hsCRP) and tumor necrosis factor α (TNF-α) [6-9]. High-sensitive CRP has been shown to be a predictor of cardiovascular events in both healthy subjects and patients with coronary disease in prospective studies [10-13].

Studies in adults have reported independent associations of serum hsCRP and TNF-α concentrations with the body mass index (BMI) [9-11,14]. It has been proven that, in adulthood, weight loss leads to a decrease of serum hsCRP concentrations and event risks [13-18], whereas studies concerning serum TNF-α concentrations in weight loss are controversial. Some studies reported decreasing TNF-α concentrations [19-23], whereas others described stable TNF-α concentrations in weight loss [17,24,25].

However, there are very few reports concerning hsCRP and TNF-α concentrations in obese children and their relationship to the BMI and cardiovascular risk factors [6,26,27]. Because adverse patterns of atherosclerosis itself begin in childhood [28], studies of population and

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0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.03.022

individual differences in the early onset and progression through childhood of possible initiating risk factors are important. The advantage of examining the inflammatory markers in children is that there is no potential confusion with coronary disease or active tobacco smoking [10,29].

Long-term studies are required to determine whether in some individuals, associations between inflammatory markers and obesity reflect long-term deviation of the risk factors or whether in other individuals, they reflect short-term fluctuation. There are no long-term studies in obese children concerning the relationships between serum hsCRP and TNF-α, insulin resistance, cardiovascular risk factors, and change in weight status. To confirm the existence of obesity-induced inflammation and to clarify the association between such inflammation and other cardiovascular risk factors, we investigated the relationship between hsCRP, TNF-α, obesity, blood pressure, lipids, and insulin resistance in a long-term follow-up of obese children.

2. Methods

We studied 14 nonobese healthy and 16 obese children who lost a substantial amount of their overweight, as well as 15 obese children without weight change over a 1-year period (see Table 1). None of the subjects had diabetes mellitus, endocrinologic disorders, hereditary diseases, or systemic inflammatory diseases. All were nonsmokers without any regular medication. Subjects with intercurrent infections and/or febrile subjects were rescheduled and examined at a time when they were not ill to control for artificially elevated hsCRP levels. No child underwent changes in his/her pubertal stage during the 1-year study period.

Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured undressed to the nearest 0.1 kg using a calibrated balance scale. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Obesity was defined according to the BMI 97th percentile reaching BMI values of 30 kg/m^2 at 18 years of age using population-specific data [30]. Because BMI is not normally distributed, we use the LMS method for calculating BMI SD score (SDS-BMI) [30,31]. The M and S curves correspond to the median and coefficient of variation BMI for German children at each age and sex, whereas the L curve allows for the substantial age-dependent variation in the distribution of the BMI. The assumption behind the LMS method is that, after Box-Cox power transformation, the data at each age are normally distributed [31].

Substantial weight loss was defined by a decrease in SDS-BMI of 0.5 or more because in previous studies, we demonstrated the improvement of insulin sensitivity and cardiovascular risk factors in German obese children only if the SDS-BMI decreased by at least 0.5 over a 1-year period [32,33]. Children without weight change were defined by a change in SDS-BMI of less than 0.05 over the 1-year period.

The pubertal developmental stage was determined according to Marshall and Tanner and categorized into 2 groups (prepubertal: boys with pubic hair and gonadal stage I, and girls with pubic hair stage and breast stage I; and pubertal: boys with pubic hair and/or gonadal stage ≥II, and girls with pubic hair stage and/or breast stage ≥II).

The following variables were measured in serum during fasting state in all children: insulin, glucose, hsCRP, TNF-α, triglyceride, and HDL-C concentrations. The children and their parents had been carefully instructed to fast over a period of at least 14 hours. High-density lipoprotein cholesterol concentrations were measured by an enzymatic test (HDL-C-Plus; Roche Diagnostics, Mannheim, Germany), and triglyceride concentrations, by a colorimetric assay using a Vitros analyzer (Ortho Clinical Diagnostics, Neckargemuend, Germany). Insulin concentrations were measured by microparticle-enhanced immunometric assay (MEIA, Abbott, Wiesbaden, Germany). Glucose levels were determined by colorimetric test using a Vitros analyzer (Ortho Clinical Diagnostics). Intra-assay and interassay coefficients of variation were <5% in all methods. Homeostasis model assessment (HOMA) [34] was used to detect the degree of insulin sensitivity in glucose metabolism. The sensitivity can be assessed from the fasting glucose and insulin concentrations by the formula: HOMA = (insulin [mU/L] × glucose [mmol/L]) / 22.5. High-sensitive CRP concentrations were measured by means of a particle-enhanced immunonephelometric assay using a BN II analyzer (Dade Behring, Marburg, Germany). The sensitivity of this assay was 0.18 mg/L. The interassay and intra-assay coefficients of variation were 3.8% (mean, 1.1 mg/L; n = 20) and 3.9% (mean, 1.3 mg/L; n = 20), respectively. Tumor necrosis factor α concentrations were determined by an immunometric assay using

Table 1
Age, weight status (BMI, SDS-BMI), pubertal stage, insulin resistance (HOMA), blood pressure, and serum insulin, glucose, lipids, hsCRP, and TNF-α concentrations in obese and nonobese children

	Obese children	Nonobese children	*P*
No.	31	14	
Age (y)	11 (9-13)	11 (10-13)	.179
Weight (kg)	62.3 (47.6-73.2)	44.5 (38.7-55.6)	.026
BMI (kg/m^2)	26.4 (24.5-28.7)	20.4 (18.3-23.2)	<.001
SDS-BMI	2.21 (2.09-2.75)	0.81 (0.48-1.16)	<.001
Sex	52% males	50% males	.922
Pubertal stage	57% prepubertal	61% prepubertal	.558
Insulin (mU/L)	17 (11-22)	9 (6-11)	<.001
Glucose (mg/dL)	89 (83-92)	82 (78-87)	.026
HOMA	3.7 (2.4-4.7)	2.7 (1.8-3.2)	.034
HDL-C (mg/dL)	46 (40-53)	55 (41-70)	.015
Triglyceride (mg/dL)	98 (61-148)	71 (62-78)	.011
SBP (mm Hg)	115 (110-122)	99 (96-109)	<.001
DBP (mm Hg)	58 (52-71)	51 (47-59)	.003
TNF-α (pg/mL)	7.8 (6.2-9.8)	6.9 (5.1-7.8)	.015
hsCRP (mg/L)	2.00 (0.50-3.06)	0.27 (0.00-0.42)	<.001

Data are presented as median and interquartile range or percentage.

an Immulite analyzer (DPC Biermann, Bad Nauheim, Germany). The sensitivity of this assay was 1.7 pg/mL. The intra-assay and interassay coefficients of variation were 3.5% (mean, 34 pg/mL; n = 20) and 5.8% (mean, 33 pg/mL; n = 20), respectively.

The blood pressure was measured using a validated protocol [35]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the arm twice after a 10-minute rest in the supine position using a calibrated sphygmomanometer and averaged thereafter. The cuff size, which was based on the length and circumference of the arm, was chosen to be as large as possible without having the elbow skin crease obstruct the stethoscope [35]. The intraoperator variability was less than 5% for SBP and DBP based on the double measurement. The intraoperator variability was less than 5% for SBP and DBP, which was calculated in 10% of the measurements. Hypertension was defined by blood pressure above the 95th percentile for age, sex, and height [35].

In the 31 obese children, all variables were measured at baseline and 1 year later after they had participated in a 1-year outpatient intervention program *Obeldicks*. This program includes physical exercise, nutrition education (high-carbohydrate, fat-reduced diet), and behavioral therapy with individual psychological care of the child and his/her family [36,37]. An interdisciplinary team of pediatricians, diet assistants, psychologists, and exercise physiologists are responsible for the training.

Statistical analysis was performed using Winstat for Excel. All continuous variables were tested for normal distribution by Kolmogorov-Smirnov test. $P < .05$ was considered statistically significant. Values are expressed as median and interquartile range. Statistically significant differences were tested for qualitative items by χ^2 test and for normally distributed quantitative items by the Student t test for paired observations as well as that for unpaired observations. Not normally distributed variables were tested by Wilcoxon test for paired observations and by Mann-Whitney U test for unpaired observations. High-sensitive CRP and tumor necrosis factor α were correlated to weight status (SDS-BMI), insulin resistance index (HOMA), blood pressure, and triglyceride and HDL-C levels in the obese and the nonobese children by Pearson correlation at baseline. Changes in hsCRP and TNF-α over the 1-year period in the obese children were correlated to changes in insulin resistance index (HOMA), blood pressure, triglyceride, and HDL-C by Pearson correlation. The study was approved by the local ethics committee of the University of Witten/Herdecke. Informed consent was obtained from all subjects and their parents.

3. Results

Insulin resistance index (HOMA), blood pressure, and glucose, insulin, lipid, TNF-α, and hsCRP concentrations of the obese and nonobese children are shown in Table 1. The obese children did not differ significantly from the nonobese children in age, sex, and pubertal status. The obese children presented significantly higher blood pressure, insulin resistance index (HOMA), and insulin, glucose, triglyceride, TNF-α, and hsCRP concentrations, whereas their HDL-C concentrations were significantly lower compared with nonobese children (see Table 1).

The 16 obese children who had achieved a substantial weight loss decreased their SDS-BMI on average by 0.66 (interquartile range, 0.54-0.79). The 15 obese children with stable weight status changed their SDS-BMI on average by 0.01 (interquartile range, −0.01 to 0.06).

The weight loss in the 16 obese children led to a significant decrease in HOMA, SBP, DBP, and hsCRP, triglyceride, and insulin concentrations, whereas there were no significant changes in TNF-α and glucose concentrations (see Table 2). High-density lipoprotein cholesterol concentrations tended to increase in this group of children.

In the 15 obese children with stable weight status, no significant changes occurred in hsCRP, TNF-α, HDL-C, and triglyceride concentrations, or in SBP and DBP (see Table 3).

The changes in hsCRP over the 1-year period in the obese children were not significantly correlated to the changes in TNF-α ($r = -0.04$, $P = .420$), HDL-C ($r = 0.12$, $P = .268$), triglyceride ($r = 0.08$, $P = .327$), and insulin levels ($r = 0.12$, $P = .265$); HOMA ($r = 0.11$, $P = .272$); SBP ($r = -0.20$, $P = .146$); and DBP ($r = -0.23$, $P = .109$). The changes in TNF-α levels over the 1-year period were not significantly correlated to the changes in HDL-C ($r = 0.02$, $P = .464$), triglycerides ($r = -0.07$, $P = .342$), and insulin levels ($r = 0.06$, $P = .381$); HOMA ($r = 0.07$, $P = .361$); SBP ($r = -0.060$, $P = .358$); and DBP ($r = 0.11$, $P = .286$).

At baseline, hsCRP did not significantly correlate to age ($r = -0.14$, $P = .170$), SBP ($r = 0.08$, $P = .309$), DBP ($r = 0.026$, $P = .434$), triglyceride ($r = 0.12$, $P = .206$), insulin ($r = 0.08$, $P = .307$), insulin resistance index (HOMA)

Table 2
Changes in weight status (BMI, SDS-BMI), blood pressure, insulin resistance (HOMA), and serum insulin, glucose, lipids, hsCRP, and TNF-α concentrations over a 1-year period in 16 obese children with substantial weight loss (decrease in SDS-BMI of ≥0.5)

	At baseline	1 y later	P
Weight (kg)	50.0 (42.1-64.7)	47.4 (38.6-60.7)	.032
BMI (kg/m^2)	25.1 (23.3-27.1)	23.0 (21.8-23.6)	<.001
SDS-BMI	2.5 (2.1-2.8)	1.8 (1.5-2.1)	<.001
HDL-C (mg/dL)	46 (41-53)	53 (48-60)	.091
Triglyceride (mg/dL)	88 (60-128)	73 (51-91)	.048
SBP (mm Hg)	112 (102-120)	100 (98-107)	.004
DBP (mm Hg)	59 (53-74)	51 (47-58)	.019
Glucose (mg/dL)	88 (82-94)	85 (82-88)	.116
Insulin (mU/L)	13 (7-17)	6 (4-11)	<.001
Insulin resistance index (HOMA)	2.9 (1.5-2.9)	1.3 (0.7-2.4)	<.001
hsCRP (mg/L)	2.3 (0.3-3.1)	0.8 (0.4-1.4)	.008
TNF-α (pg/mL)	8.3 (6.3-9.8)	8.2 (6.7-9.1)	.546

Data are presented as median and interquartile range.

Table 3
Changes in weight status (BMI, SDS-BMI), blood pressure, insulin resistance (HOMA), and serum insulin, glucose, lipids, hsCRP, and TNF-α concentrations over a 1-year period in 15 obese children with stable weight status

	At baseline	1 y later	*P*
Weight (kg)	71.2 (66.1-76.4)	78.5 (71.6-84.5)	<.001
BMI (kg/m^2)	27.6 (26.2-29.0)	28.1 (26.4-31.2)	<.001
SDS-BMI	2.2 (2.1-2.5)	2.2 (2.1-2.5)	.604
HDL-C (mg/dL)	47 (37-54)	42 (38-52)	.154
Triglyceride (mg/dL)	125 (76-153)	110 (85-151)	.497
SBP (mm Hg)	121 (111-125)	121 (111-122)	.440
DBP (mm Hg)	58 (51-66)	62 (60-81)	.191
Glucose (mg/dL)	89 (87-91)	88 (83-90)	.232
Insulin (mU/L)	22 (17-25)	19 (15-25)	.384
Insulin resistance index (HOMA)	4.7 (3.7-5.4)	3.9 (3.1-5.8)	.339
hsCRP (mg/L)	1.3 (0.9-3.3)	0.6 (0.4-4.7)	.591
TNF-α (pg/mL)	6.8 (5.3-8.9)	6.8 (5.4-8.9)	.593

Data are presented as median and interquartile range.

(r = 0.01, P = .471), and TNF-α (r = 0.20, P = .098), whereas hsCRP significantly correlated to SDS-BMI (r = 0.28, P = .029) and HDL-C (r = −0.35, P = .010). Tumor necrosis factor α significantly correlated to age (r = −0.35, P = .010) and SDS-BMI (r = 0.32, P = .017), whereas TNF-α did not significantly correlate to SBP (r = −0.17, P = .150) and DBP (r = −0.13, P = .216), HDL-C (r = −0.20, P = .100), triglyceride (r = 0.23, P = .066), insulin (r = 0.08, P = .295), and insulin resistance index (HOMA) (r = −0.03, P = .491).

The hsCRP levels did not significantly differ (P = .108) between the 22 prepubertal (median hsCRP, 1.1 mg/L; interquartile range, 0.3-3.0 mg/L) and the 23 pubertal children (median hsCRP, 0.5 mg/L; interquartile range, 0-2.1 mg/L), whereas TNF-α concentrations were significantly (P = .038) higher in prepubertal children (median TNF-α, 7.8 pg/mL; interquartile range, 6.4-10.0 pg/mL) compared with the pubertal children (median TNF-α, 6.8 pg/mL; interquartile range, 5.3-8 pg/mL).

The hsCRP levels did not significantly differ (P = .724) between the 21 boys (median hsCRP, 0.9 mg/L; interquartile range, 0.3-2.3 mg/L) and the 24 girls (median hsCRP, 0.6 mg/L; interquartile range, 0-3.2 mg/L). The TNF-α levels did not differ significantly (P = .946) between the 21 boys (median TNF-α, 7.7 pg/mL; interquartile range, 6.2-8.7 mg/L) and the 24 girls (median TNF-α, 6.9 pg/mL; interquartile range, 5.2-8.8 mg/L).

4. Discussion

The present study is the first to not only analyze the cross-sectional relationships between hsCRP, TNF-α, cardiovascular risk factors, insulin resistance, and degree of overweight in children, but also the long-term changes in these parameters. Obese children demonstrated significantly higher serum concentrations of hsCRP, TNF-α, triglyceride and insulin; insulin resistance index (HOMA); and blood pressure compared with nonobese children of the same age, sex, and pubertal status. Weight loss in the obese children was associated with a significant decrease of these parameters except for TNF-α.

The positive correlations between hsCRP and weight status (SDS-BMI) are in agreement with other studies in children and adolescents [6,27,29,38-41]. This could be explained by the fact that the main regulator of the syntheses of CRP in the liver is the adipocyte-derived proinflammatory cytokine interleukin 6 (IL-6) [9,42-44].

High-sensitive CRP levels decreased significantly in the group of obese children with weight loss as reported in studies in adults [15,45]. A tendency without significance of decreasing hsCRP could also be measured in the obese children with stable weight in our study. This could be explained by these obese children participating in an intervention program that included physical exercise. Physical fitness and activity have been reported to have a minor independent effect on CRP levels [29,38].

Weight loss was associated with an improvement of cardiovascular risk factors (hypertension, dyslipidemia, and insulin resistance index) in agreement with other studies in childhood [32,33]. Some cross-sectional studies reported a relationship between hsCRP and the other cardiovascular risk factors [16,46,47]. In contrast, hsCRP did not correlate to blood pressure, lipids, and insulin resistance index (HOMA) in cross-sectional analyses in our study, and consistently and most importantly, changes in hsCRP did not correlate to changes in blood pressure, lipids, and insulin resistance index. A narrow range of variation in the changes observed in CRP and metabolic variables may explain the lack of significant correlation between these variables in our relatively small sample size with moderate weight loss. On the other hand, a previous longitudinal study in obese adults also reported that changes in CRP were not related to insulin resistance [18]. The correlations between CRP and most cardiovascular risk factors in cross-sectional analyses could be largely explained by the confounding effect of obesity, which is independently associated with all cardiovascular risk factors [29]. These data suggest that hsCRP may be independent of the other cardiovascular risk factors [29,40].

Chronic inflammation plays a role in the progression and initiation of atherothrombotic disease [48]. C-reactive protein stimulates the uptake of low-density lipoprotein by macrophages, induces complement activation, enhances infiltrations of monocytes, and stimulates tissue factor production, thus enhancing the risk for thrombosis and the generation of atherosclerosis lesions [13,49-51]. Accordingly, hsCRP values in the blood are a good indicator for the likelihood of acute coronary and cerebral events [7,13,52]. Intima-media thickness in obese children was associated with serum hsCRP levels [41,53].

Tumor necrosis factor α correlated significantly to weight status (SDS-BMI) in agreement with a previous study in adolescence [26]. This could be explained by the fact that

TNF-α is secreted by adipose tissue [25,26,42,43]. Tumor necrosis factor α levels did not decrease in obese children who lost weight, which is in agreement with 3 studies in adults [17,24,25] and in contrast to 5 studies in adults demonstrating decreasing TNF-α levels in weight loss [19-23]. The small sample sizes and the relatively small difference in TNF-α levels between obese and nonobese children may explain the lack of a significant decrease in TNF-α levels in the obese children who lost weight in our study. A too low degree of weight loss seems unlikely because all other cardiovascular risk factors, including hsCRP, improved in the obese children with weight loss. Probably, other factors that influence TNF-α levels such as age, pubertal status, and fat distribution might present relevant aberrations. For instance, TNF-α is only secreted in omental but not in subcutaneous fat [42].

Some cross-sectional studies demonstrate relationships between TNF-α and insulin resistance, blood pressure, and HDL-C [18,21,26,42,47]. In contrast, TNF-α did not correlate to blood pressure, lipids, and insulin resistance index (HOMA) in our cross-sectional analyses, and consistently and most importantly, changes in TNF-α did not correlate to changes in blood pressure, lipids, and the insulin resistance index (HOMA). A narrow range of variation in the changes observed in TNF-α and metabolic variables may explain the lack of significant correlation between these variables in our relatively small sample size with moderate weight loss. A previous study investigating the relationship between TNF-α and insulin resistance in childhood also found no correlation between TNF-α and insulin resistance [54]. Therefore, TNF-α is probably independent of the other cardiovascular risk factors.

The association of CRP and TNF-α with the indices of obesity and atherosclerosis may reflect the role of cytokines in mediating the metabolic effects of obesity. The adipose tissue–derived IL-6, the main regulator of the syntheses of CRP in the liver [9,42-44], presents such a mediator and is a further marker of chronic inflammation [25,42,55]. Tumor necrosis factor α is itself a potent inducer of IL-6 production [56]. Thus, measurement of IL-6 in obese children losing weight as an alternative marker of chronic inflammation seems interesting.

Our study presents some potential limitations. First, some studies reported on a relationship between age and CRP levels [29,38,40], probably influencing the CRP levels over the 1-year period. However, this relationship was reported to be only very weak, whereas other studies demonstrated no relationship between age and CRP levels, which is in agreement with our findings [6,57]. Second, seasonal variations in CRP have been clearly demonstrated and attributed to seasonal variations in minor respiratory tract infections [57]. Because we measured CRP over a 1-year period, a seasonal variation appears unlikely. Third, low-grade infections may have influenced the CRP levels. Children generally were not examined when acutely ill or febrile. Furthermore, CRP is rarely elevated in uncomplicated upper respiratory tract infections. It has been demonstrated that low-grade inflammation does not result from asymptomatic infection in obesity [58]. Fourth, the HOMA model is only an assessment of insulin resistance. Clamp studies are the gold standard to analyze insulin resistance. Because the HOMA model correlated to clamp studies, it is a good method to examine insulin resistance in field studies [59]. Finally, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measure of fat mass.

In summary, obese children demonstrated significantly higher serum concentrations of hsCRP and TNF-α compared with nonobese children. The chronic inflammation markers TNF-α and hsCRP were independent of lipids, blood pressure, and insulin resistance both in cross-sectional and longitudinal analyses. Weight loss was associated with a significant decrease of hsCRP, triglyceride levels, and blood pressure. Long-term studies are required to examine whether this improvement of cardiovascular risk factors will eventually lead to a significant clinical benefit in regard to cardiovascular morbidity and mortality.

Acknowledgment

We thank Ms Martina Schmidt for the excellent technical assistance in performing the hsCRP and TNF-α assays.

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