The mechanism by which TNF-α (tumour necrosis factor-α) may cause insulin resistance is not clear. On the basis of experiments in rats, TNF-α has been suggested to cause defects in capillary function, with a decreased access of insulin and glucose to tissues. To test this hypothesis in humans, we assessed serum TNF-α concentrations, skin capillary recruitment and insulin sensitivity in a group of 37 healthy adults. In addition, we measured these variables in 21 of their prepubertal children. Serum TNF-α levels were measured by sandwich enzyme immunoassay, and insulin sensitivity was assessed with the hyperinsulinaemic euglycaemic clamp technique. Capillary recruitment during post-occlusive reactive hyperaemia was evaluated by videomicroscopy. In the adults, serum TNF-α levels were associated with both capillary recruitment \( r = -0.40, P = 0.02 \) and insulin sensitivity \( r = -0.33, P = 0.05 \). In addition, capillary recruitment was associated with insulin sensitivity \( r = 0.34, P = 0.04 \). Regression analysis showed that the association between TNF-α and insulin sensitivity \( [-0.527 \text{ mg} \cdot \text{kg}^{-1} \text{ of body weight} \cdot \text{min}^{-1} \text{ per pmol/l per pg/ml TNF-α (95% confidence interval, -1.066 to 0.011)}; P = 0.05] \) decreased by 30% after adjustment for capillary recruitment. In the children, neither capillary recruitment \( r = -0.33, P = 0.2 \) nor insulin sensitivity \( r = -0.24, P = 0.4 \) was significantly associated with TNF-α. In conclusion, in adults, but not in children, serum TNF-α levels are associated with capillary recruitment during post-occlusive hyperaemia, which, in part, can explain the relationship between TNF-α and insulin resistance. Our data suggest that these relationships are initiated during growth from childhood to adulthood.

Key words: body mass index, capillary recruitment, microcirculation, insulin resistance, tumour necrosis factor (TNF).

Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variation; IQR, interquartile range; SNP, sodium nitroprusside; TNF-α, tumour necrosis factor-α.

1Both authors contributed equally to this study.

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INTRODUCTION

The inflammatory cytokine TNF-α (tumour necrosis factor-α) has been reported to play an important role in the insulin resistance of obesity, Type II diabetes and sepsis [1,2]. Several studies have demonstrated that high levels of TNF-α mRNA and protein are associated with insulin resistance in adult animals and humans [3–7]. In addition, administration of TNF-α to animals can induce insulin resistance [8,9] and, although neutralization of TNF-α was not associated with an improved insulin sensitivity in patients with diabetes [10], inhibition of TNF-α can improve insulin sensitivity in animals [3,11].

The mechanism by which TNF-α may cause insulin resistance is not clear. Studies in isolated cells have shown that TNF-α has direct effects on the insulin signalling cascade [12,13]; however, these effects could not be found in isolated skeletal muscle [14]. As an alternative, experiments in rats have suggested that TNF-α causes defects in microvascular function, in particular insulin-induced capillary recruitment, with a decreased access of insulin and glucose to tissues [15].

An important role of microvascular function as a partial explanation for the demonstrated defects in the ability of insulin to increase glucose uptake, limb blood flow and blood volume in insulin-resistant states has been suggested by several animal and human studies [16–20]. In rats, insulin has been shown to cause capillary recruitment in hind-leg muscles [16], and changes in insulin-induced capillary recruitment were associated with changes in insulin-mediated glucose uptake [17]. In humans, we have demonstrated [21] that insulin infusion induced capillary recruitment in human skin, and this insulin-induced capillary recruitment was associated with the degree of capillary recruitment during post-occlusive hyperaemia. Capillary recruitment after post-occlusive reactive hyperaemia, as well as microvascular endothelium-dependent vasodilation in skin, has been shown to be associated with the metabolic and vascular actions of insulin in both normal and hypertensive individuals [22,23].

Therefore elevated levels of TNF-α may be associated with impaired microvascular function in humans, which may decrease the delivery of glucose and insulin to skeletal muscle, and play a role in the link between TNF-α and insulin resistance. To test this hypothesis, we assessed serum TNF-α concentrations, microvascular function [i.e. skin capillary recruitment during post-occlusive reactive hyperaemia and endothelium-(in)dependent vasodilation] and insulin sensitivity in a group of 37 healthy adult individuals. Growth may play an important role in the development of insulin sensitivity and its determinants [24]. Several studies have shown that relationships among cardiovascular risk factors and vascular function are initiated and/or amplified during growth [25–31].

To investigate the influence of growth on the associations between TNF-α concentrations, capillary recruitment and insulin resistance, we compared the adult individuals with 21 of their children.

MATERIAL AND METHODS

Study population

This study was part of a larger ongoing project in which vascular and metabolic variables were studied in prepubertal children [32] and their parents. They were recruited from the same catchment area and the children had been born at the VU University Medical Center in Amsterdam. Families still living at the same address were contacted by letter and phone. All family members were of Caucasian origin. The present study investigates the relationships between TNF-α, skin capillary recruitment during post-occlusive reactive hyperaemia and insulin sensitivity. After exclusion of subjects with non-insulin-dependent diabetes mellitus, recent vaccinations and rheumatoid arthritis, 37 healthy adult individuals and 21 children participated in this study. Characteristics of the individuals are summarized in Table 1. We excluded children that were in puberty by using the Tanner stages, i.e. testicle volume < 3 ml in boys and breast development M1 in girls.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee. Informed consent was obtained from each adult. For the children, written informed consent was obtained from both parents and verbal informed consent was obtained from the children.

Measurements

Microvascular measurements were conducted in the morning after 30 min of acclimatization in a quiet temperature-controlled room (23.4 ± 0.4 °C), with the individuals in the sitting position and the investigated nondominant hand at heart level. All individuals abstained from caffeine-containing drinks overnight. Nailfold and iontophoresis studies were performed on the same day. Microvascular and metabolic studies (see below) were carried out on separate days approx. 1 week apart and were performed by two different investigators. Both investigators were blinded to the results of the tests performed by the other investigator.

Perfused nailfold capillaries in the dorsal skin of the third finger were visualized by a capillary microscope, as described previously [22,23,33]. Two separate visual fields of 1 mm² were recorded before and after 4 min of arterial occlusion with a digital cuff, and the images were stored on videotape. Capillaries were visualized approx. 1.5 mm proximal to the terminal row of capillaries in the middle of the nailfold of the third finger. At this spot, capillaries are located perpendicular to the skin and
Table 1 Characteristics of the parents and the children

Data are presented as means ± S.D. or as medians (IQR)*. †P < 0.001 compared with baseline. PRH, post-occlusive reactive hyperaemia.

<table>
<thead>
<tr>
<th></th>
<th>Parents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male/female)</td>
<td>37 (21/16)</td>
<td>21 (11/10)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.5 ± 4.9</td>
<td>8.6 ± 1.2</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>87.8 ± 12.2</td>
<td>57.9 ± 8.8</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>100.8 ± 7.8</td>
<td>70.3 ± 8.6</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.82 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.80 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.75 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.9 ± 9.1</td>
<td>136.6 ± 8.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.0 ± 14.8</td>
<td>30.7 ± 7.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 5.3</td>
<td>26.0 ± 2.6</td>
</tr>
<tr>
<td>Men</td>
<td>23.9 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>25.3 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>58.3 ± 11.5</td>
<td>22.9 ± 4.1</td>
</tr>
<tr>
<td>24-h Systolic blood pressure (mmHg)</td>
<td>122.7 ± 15.9</td>
<td>111.4 ± 11.9</td>
</tr>
<tr>
<td>24-h Diastolic blood pressure (mmHg)</td>
<td>76.0 ± 9.8</td>
<td>65.0 ± 8.3</td>
</tr>
<tr>
<td>24-h Heart rate (beats/min)</td>
<td>61.2 ± 11.2</td>
<td>81.4 ± 8.5</td>
</tr>
<tr>
<td>Inulin sensitivity (mg · kg⁻¹ of body weight · min⁻¹ per pmol/l) × 100</td>
<td>1.70 ± 1.17</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>Capillary recruitment during PRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline capillary density (per mm²)</td>
<td>45.1 ± 11.1</td>
<td>39.8 ± 6.6</td>
</tr>
<tr>
<td>Peak capillary density (per mm²)</td>
<td>61.6 ± 16.4</td>
<td>52.5 ± 11.7</td>
</tr>
<tr>
<td>Capillary recruitment (%)</td>
<td>38 ± 24</td>
<td>33 ± 24</td>
</tr>
<tr>
<td>Acetylcholine-mediated vasodilation (%)</td>
<td>337 ± 132</td>
<td>424 ± 270</td>
</tr>
<tr>
<td>SNP-mediated vasodilation (%)</td>
<td>298 ± 198</td>
<td>319 ± 208</td>
</tr>
<tr>
<td>TNF-α (μg/ml)</td>
<td>2.07 ± 0.70</td>
<td>5.1 (2.7–7.6)*</td>
</tr>
</tbody>
</table>

occlusive reactive hyperaemia by the capillary density in the resting state. Intrasubject CV (coefficient of variation) was 17.2 ± 12.1 % (measured on two occasions in seven individuals).

Endothelium-dependent and -independent vasodilatation of skin microcirculation was evaluated by iontophoresis of acetylcholine and SNP (sodium nitroprusside) in combination with laser Doppler fluxmetry as described previously [22,23]. The Perimed iontophoresis system was used. Acetylcholine, dissolved in 3 % (v/v) mannitol in water (1 % acetylcholine; Miochol; Bournonville Pharma), was delivered using an anodal current; seven doses (0.1 mA for 20 s) were delivered, with a 60-s interval between each dose. SNP, dissolved in water for injection (0.1 % SNP; Nipride; Roche), was delivered using a cathodal current; nine doses (0.2 mA for 20 s) were delivered, with a 90-s interval between each dose. Acetylcholine-dependent laser Doppler flux was measured on the middle phalanx of the third finger, whereas SNP-dependent laser Doppler flux was measured on the middle phalanx of the fourth finger. Approx. 15 min elapsed between these two measurements. The responses to acetylcholine and SNP were calculated as the percentage increase from baseline to the plateau phase (during the final two iontophoretic deliveries). Intrasubject CV of the percentage increase from baseline to the plateau phase (final two iontophoretic deliveries) was 13.5 ± 7.7 % for acetylcholine and 18.7 ± 23.4 % for SNP (measured on two occasions in seven subjects). Our previous studies in adults have shown that the non-specific effects do not play an important role in the relationships between microvascular function, blood pressure and the vascular and metabolic actions of insulin [21,22]. To exclude possible non-specific microcirculatory reactivity in children, responses to the vehicles of both acetylcholine (3 % mannitol) and SNP (water for injection) were tested in six of the children. In these children, both acetylcholine and SNP vehicle elicited a small, but non-significant, increase in blood flow [median, 9 % (P = 0.1) and 37 % (P = 0.1) respectively].

Sensitivity to insulin-mediated glucose uptake was assessed by the hyperinsulinaemic euglycaemic clamp technique, as described previously [22]. Briefly, insulin (Velosulin; Novo Nordisk) was infused in a primed continuous manner at a rate of 60 munits · kg⁻¹ of body weight · h⁻¹ for 2 h. Normoglycaemia was maintained by adjusting the rate of a 20 % d-glucose infusion based on plasma glucose measurements performed at 5-min intervals. Whole body glucose uptake (M) was calculated from the glucose infusion rate during the last 60 min and expressed per unit of plasma insulin concentration (M/I) [35]. Plasma insulin concentrations were measured by RIA (Immunoradiometric Assay; Medgenix Diagnostics). For convenience the M/I ratio was multiplied by 100. Children were informed extensively of what was going to happen and cartoons were created to explain the
tests to the children. We performed the clamp in the child together with the clamp in one of the parents in the same room at the same time. The clamp technique was tolerated well by all parents and children.

Anthropometric measurements (which included weight, height, waist circumference and hip circumference) were performed on all participants by a trained investigator as described previously [22]. BMI (body mass index) was calculated by dividing the weight (in kg) by the height (in m²). The waist-to-hip ratio was calculated as a measure of body fat distribution. Fat-free mass was measured using a four-terminal bioimpedance analyser (RJL Spectrum Bioelectrical Impedance BIA 101/S Akern, RJL-System) and equations based on total body water [36,37].

Human TNF-α was measured by sandwich enzyme immunoassay (Quantikine High Sensitivity; R&D Systems). The intra- and inter-assay CV for TNF-α were 7.3 and 8.8% respectively.

Statistical analysis
Variables are presented as means ± S.D., or in case of a skewed distribution as medians and IQR (interquartile range). In adults, partial correlation analyses were used to investigate the relationships between serum TNF-α, capillary recruitment, insulin sensitivity and measures of obesity after adjustment for age and sex. Subsequently, a multiple regression analysis was used to analyse whether the association between TNF-α concentrations and insulin sensitivity remained when allowing for capillary recruitment. In children, the partial correlations were not adjusted for age and sex. Multiple regression analysis requires that the measurements be independent. Because our study of 37 adults includes 16 couples, the restriction of independence may not be met and TNF-α levels may correlate positively among spouses. We, therefore, investigated the correlation of TNF-α in the fathers with that in the mothers. Higher TNF-α levels in the father were not related to higher TNF-α levels in the mother (r = -0.31, P = 0.2). Therefore, in the subsequent analyses, TNF-α measurements were treated as independent. Interaction analyses were performed to investigate whether the associations were different between the adults and children after adjustment for age and sex. For the linear regression analyses in children and in the combined population of adults and children, TNF-α levels were log-transformed to achieve a normal distribution. A two-tailed P value of < 0.05 was considered significant. All analyses were performed using the statistical software package SPSS version 9.0.

RESULTS

In the adults, the mean serum TNF-α concentration was 2.0 ± 0.7 pg/ml (Table 1). In the children, TNF-α showed a skewed distribution. The median TNF-α concentration was 5.1 pg/ml (IQR, 2.7–7.6 pg/ml). During the hyper-insulinaemic euglycaemic clamp, glucose levels were maintained at 5.0 ± 0.2 mmol/l. Attained serum free insulin concentrations averaged 523 ± 145 pmol/l in the adults and 330 ± 159 pmol/l in the children. The mean rate of glucose uptake, expressed per kg of body weight (M value), was 7.9 ± 0.7 and 10.1 ± 4.2 mg · kg⁻¹ · body weight · min⁻¹ in the adults and children respectively. Table 1 shows the insulin sensitivity expressed as whole-body glucose uptake per kg of body weight per min per unit of plasma insulin concentration (mg · kg⁻¹ · body weight · min⁻¹ per pmol/l).

Table 2 Correlation analysis of TNF-α, capillary recruitment, insulin sensitivity and features of obesity in 37 adult individuals after adjustment for age and sex

<table>
<thead>
<tr>
<th></th>
<th>TNF-α</th>
<th>Insulin sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>0.33</td>
<td>0.05</td>
</tr>
<tr>
<td>Capillary recruitment</td>
<td>0.40</td>
<td>0.02</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.15</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI</td>
<td>0.29</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Correlation and linear regression analyses

In the adults, the correlation coefficients were adjusted for age and sex. Resting capillary density was not related to TNF-α (r = -0.05, P = 0.8) or insulin sensitivity (r = -0.06, P = 0.7). However, TNF-α concentrations were associated with both capillary recruitment and insulin sensitivity (Table 2 and Figure 1). Capillary recruitment was associated with insulin sensitivity (Table 2 and Figure 1). TNF-α was not associated with the waist-to-hip ratio (Table 2), but was positively associated with BMI (P = 0.09; Table 2). Subsequently, we investigated whether the association between TNF-α and insulin sensitivity could be explained by capillary recruitment (Table 3). Model 1 shows that TNF-α (independent variable), after adjustment for age and sex, was related to insulin sensitivity (dependent variable). In addition, after adjustment for age and sex, an increase in TNF-α of 1 pg/ml was associated with a decrease in capillary recruitment of 13 % points [95% CI (confidence interval), −23 to −2; P < 0.05]. This association was similar after adjustment for BMI [11% points per pg/ml TNF-α (95% CI, −21 to −0.1); P < 0.05]. Model 2 shows that, after adjustment for capillary recruitment, the regression coefficient of the association between TNF-α and insulin sensitivity decreased by 30% and was no longer statistically significant (Table 3). This suggests that, at least statistically, capillary recruitment may partly explain the relationship between TNF-α and insulin sensitivity. After additional adjustment for BMI, the association between TNF-α and insulin sensitivity was
After adjustment for age and sex, the correlation coefficients were $-0.33 (P = 0.05)$ for the association between TNF-$\alpha$ and insulin sensitivity, $-0.40 (P = 0.02)$ for the association between TNF-$\alpha$ and capillary recruitment, and $-0.34 (P = 0.04)$ for the association between capillary recruitment and insulin sensitivity. Without adjustment for age and sex, the correlation coefficients were $-0.32 (P = 0.06)$, $-0.37 (P = 0.02)$ and $-0.28 (P = 0.09)$ respectively.

In the children, TNF-$\alpha$ was not significantly associated with capillary recruitment, insulin sensitivity or measures of obesity (Table 4). If anything, the association of TNF-$\alpha$ with capillary recruitment and BMI was opposite to that in the parents. Interaction analyses suggested that the associations of TNF-$\alpha$ with capillary recruitment ($P = 0.01$) and BMI ($P = 0.09$) were different between adults and children. The association of TNF-$\alpha$ with insulin sensitivity was not clearly different between adults and children ($P = 0.3$).

TNF-$\alpha$ was not significantly associated with acetylcholine- or SNP-mediated vasodilation in the adults ($r = -0.06, P = 0.7$ and $r = 0.01, P = 0.9$ respectively) or the children ($r = 0.07, P = 0.8$ and $r = 0.26, P = 0.3$ respectively).

Skin temperature was not different between children and adults ($30.81 \pm 1.0 \degree C$ compared with $31.15 \pm 0.9 \degree C$; $P = 0.2$). Similar conclusions were reached when statistical analyses were performed using different indices of insulin sensitivity (M value, M/I value or M/I value per kg of fat-free mass). The same held true for the absolute compared with percentage increase in capillary density. The associations were not significantly different between men and women or between boys and girls (results not shown).

**DISCUSSION**

The central novel finding of the present study was the inverse association between TNF-$\alpha$ and capillary recruitment in adults. Importantly, our results confirm the...
inverse relationship of TNF-α with insulin sensitivity [6,38,39] as well as the positive relationship of insulin sensitivity with capillary recruitment [22,23]. Subsequent regression analyses were consistent with the hypothesis that the relationship between TNF-α and insulin sensitivity in adults might be explained, at least in part, by capillary recruitment.

To our knowledge, this is the first study to report the associations of TNF-α with microvascular function, insulin sensitivity and measures of obesity in children. These associations were less clear or in the opposite direction to those in their parents. The association between TNF-α and insulin sensitivity was not clearly different between adults and children. However, the association between TNF-α and capillary recruitment in children was in the opposite direction and significantly different from that in adults, which suggests that, in contrast with adults, microvascular mechanisms do not play an important role in the TNF-α-insulin sensitivity relationship in children. In addition, the association between TNF-α and BMI in adults was clearly different from that in children. Taken together, our cross-sectional findings in two different age groups suggest, therefore, that the relationships between TNF-α, vascular function, insulin sensitivity and obesity are initiated during growth from childhood to adulthood.

Interestingly, the initiation of relationships of certain variables with haemodynamic phenomena during growth has also been observed in investigations of the fetal origins hypothesis. For example, the association of birth weight with blood pressure and insulin resistance is weak or absent in children and much stronger in adults [25–30]. In addition, puberty is an important contributor to the development of Type II diabetes and cardiovascular risk [24], whereas Elhadd et al. [31] have shown that puberty modulates microvascular endothelial function and antioxidant mechanisms in childhood diabetes. Our finding that that the relationships between TNF-α, vascular function, insulin sensitivity and obesity are initiated during growth from childhood to adulthood fits with this concept.

The mechanism explaining the association between TNF-α and insulin resistance is not clear. Although studies in isolated cells have shown that TNF-α has direct effects on the insulin signalling cascade [12,13], it has also been suggested that TNF-α causes defects in capillary function, with a decreased access of nutrients to tissues. In the present study, capillary recruitment was related to both TNF-α and insulin sensitivity. Moreover, it explained statistically part of the association between TNF-α and insulin sensitivity. These cross-sectional findings in humans are consistent with the experimental data of Youd et al. [15] in rats, who demonstrated that infusion of TNF-α impaired the insulin-induced capillary recruitment and glucose uptake in skeletal muscle. Taken together, these data suggest that the association between TNF-α and insulin resistance is, in part, explained by vascular mechanisms and, in part, by direct effects of TNF-α on the insulin signalling cascade in muscle cells.

Levels of TNF-α as measured in the circulation are low and it is not known whether circulating TNF-α levels are biologically active. Nevertheless, several studies have shown an inverse relationship between plasma levels of TNF-α with insulin sensitivity [6,38,39], a concept supported further by studies demonstrating associations between TNF-α mRNA and insulin resistance [41,42] and by animal studies demonstrating that administration and/or neutralization of TNF-α have direct effects on insulin resistance [3,8,9,11]. Taken together, these data suggest that circulating TNF-α levels provide information that is useful to study the link between TNF-α and insulin resistance. Circulating TNF-α may either be a marker of the amount of TNF-α that is produced locally or synergistically with locally produced TNF-α.

The contribution of circulating TNF-α levels to the variation in insulin sensitivity in adults is only modest (12%). This finding suggests that other mechanisms are also of importance in the development of insulin resistance. On the other hand, the contribution of TNF to insulin resistance may be underestimated due to the fact that circulating levels of TNF-α may not be a very strong indicator of locally active TNF-α.

TNF-α infusion is associated with an impaired endothelium-dependent vasodilation in large vessels in animals [43] and resistance vessels in humans [44]. A reduced endothelium-dependent vasodilation at the precapillary level may be the cause of changes in capillary recruitment [34]. Our findings of an association of TNF-α levels with capillary recruitment, but not with microvascular endothelium-dependent vasodilation, do not support this mechanism, at least not with respect to the TNF-α–capillary recruitment relationship. Therefore we suggest that there is a direct association between TNF-α and the functional or structural characteristics of the capillary network, as assessed by capillary recruitment during post-occlusive reactive hyperaemia.

Although acute infusion of TNF-α, while impairing endothelium-dependent vasodilation, increases total forearm blood flow [44], this does not exclude a role for TNF-α in impairing capillary recruitment. Several studies have shown that it is capillary flow, and not total limb blood flow, that is important in the determination of insulin sensitivity [16,17,20,45].

It has been suggested that adipose tissue is a significant source of serum TNF-α. In vitro release of TNF-α by adipocytes has been reported and circulating concentrations of TNF-α have been found to be associated with BMI [46], a finding compatible with our data. Although our finding that TNF-α was not related to the waist-to-hip ratio is in contrast with findings in healthy elderly individuals and a study in obese women [39,46], it is in accordance with a study by Nilsson et al. [6], who
demonstrated in elderly men that TNF-α concentrations were associated with BMI, but not with the waist-to-hip ratio. This may be related to the relatively low amount of visceral fat in our middle-aged individuals. A relatively low amount of visceral compared with peripheral fat mass may result in a more pronounced association of TNF-α with BMI than with the waist-to-hip ratio. Additional adjustment for BMI reduced the association between TNF-α and insulin sensitivity further. This may indicate that, besides capillary recruitment, obesity-related mechanisms play a role in the TNF-α-insulin resistance relationship, but we cannot exclude that this statistical analysis resulted in over-adjustment, i.e. underestimated the remaining association between TNF-α and insulin sensitivity.

It should be emphasized that any interpretation of our results must take into account the cross-sectional design of our study. However, intervention studies in animals with administration and/or neutralization of TNF-α suggest a direct link between TNF-α, insulin resistance [3,8,9,11] and insulin-mediated capillary recruitment [15].

In conclusion, we have demonstrated that serum TNF-α is associated with capillary recruitment during post-occlusive hyperaemia in adults. In addition, this capillary recruitment can partly explain the relationship between TNF-α and insulin resistance described previously. Our findings thus provide support for a vascular component of TNF-α-induced insulin resistance. These associations, however, were not present in the prepubertal children of these adults. Our findings therefore suggest that the relationships between TNF-α, vascular function and insulin sensitivity are initiated during growth from childhood to adulthood.

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