Obesity and type 2 diabetes mellitus (DM2) have been associated with subclinical inflammation. Markers of inflammation, like the cytokine IL-6 and the acute-phase protein C-reactive protein (CRP), are elevated in obese, insulin-resistant subjects (1–3). Also TNF-α receptors, as markers for TNF-α action (4), and to a lesser extent TNF-α itself, have been found to be elevated in patients with DM2 (3) and, in some studies, also in subjects with impaired glucose tolerance (IGT), a prediabetic state (5). IL-6 is a cytokine that is produced by many cell types and is increased in cancer cachexia (6), after endotoxin stimulation (7) and after vaccination (8). IL-6 is also increased in obesity, insulin resistance, and DM2, and plasma IL-6 has been shown to be predictive of the development of DM2 in several prospective studies (9, 10). So, besides its role in inflammation, IL-6 may also affect insulin sensitivity or glucose metabolism.

It was suggested that IL-6 may cause insulin resistance in organs like liver and skeletal muscle. In human HepG2 cells and primary mouse hepatocytes, IL-6 has been shown to impair insulin signaling by reducing the tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and reducing the association of the p85 subunit of phosphatidylinositol 3-kinase with IRS-1 (11). Insulin receptor autophosphorylation and IRS-1 tyrosine phosphorylation were also reduced in vivo in the livers of mice after chronic infusion with IL-6 (12). On the other hand, in the same study, no effect was found on skeletal muscle. In addition, IL-6 administration to myocytes in culture had no effect on insulin action (13) and a short-term infusion of IL-6 in rats did not affect insulin sensitivity or whole-body glucose uptake (14). A study with healthy young men showed that the infusion of high amounts of recombinant human IL-6 did not alter glucose uptake or oxidation. This shows that acute high concentrations of IL-6 might not disturb insulin sensitivity or glucose disposal in skeletal muscle in healthy subjects (15).

The observation that increased IL-6 concentrations are associated with DM2 leads to the suggestion that the systemic production of IL-6 is increased in the insulin-resistant state. It is known that adiposity plays a role in subclinical inflammation, because adipose tissue produces inflammation markers like IL-6 (16). Recently however, the skeletal muscle has become an interesting organ in the production of IL-6 as well, because it released IL-6 during and after exercise (17, 18). So far, few studies addressed the role of muscle IL-6 production in man in the development of insulin resistance.
in conditions like IGT and DM2. During exercise, no significant differences were found in muscle IL-6 production in skeletal muscle between controls and DM2 patients (19). However, an important stressor next to exercise is the intake of a high-fat meal. In particular in DM2, the impaired handling of substrates in the postprandial phase may be of importance in the development or deterioration of insulin resistance and hyperglycemia. It has been found before that venous IL-6 concentrations increased after a high-fat meal in obese men (20). Additionally, it has been shown that after a high-fat meal, the venous IL-6 concentrations slightly increased in healthy overweight subjects, and increased even more in newly diagnosed diabetic subjects (21).

The aim of this study was to examine 1) whether skeletal muscle produces IL-6 during fasting or in the postprandial phase; 2) whether the production of IL-6 by skeletal muscle is increased in obese men with IGT compared with obese men with NGT; and if so, 3) whether the production of IL-6 in skeletal muscle changes after weight loss in IGT men. In parallel with IL-6, other inflammatory markers like CRP and TNF-α receptors were monitored.

**Subjects and Methods**

**Subjects**

Eleven obese men with IGT and nine obese men with normal glucose tolerance (NGT) matched for age and body mass index (BMI) participated in the study. Inclusion criteria were obesity (BMI > 30 kg/m²), diastolic blood pressure less than 100 mm Hg, no major health problems, and no use of medication that could influence the measurements. The IGT men had no family history of diabetes. Subjects were not involved in any regular physical activity for more than 3 h a week. The participants were asked not to change their physical activity and smoking habits during the study. One IGT person smoked. The experimental protocol was approved by the local Medical Ethical Committee of the Maastricht University. All subjects gave written informed consent.

**Glucose tolerance, body composition, aerobic capacity, and insulin sensitivity**

Subjects were screened for glucose metabolism with a standard oral glucose tolerance test (75 g glucose) with capillary blood sampling at baseline and after 2 h. Subjects were included according to the World Health Organization criteria of 1999 for capillary plasma (IGT: fasting <7.0 mmol/liter, 2 h postload >7.9 and <12.2 mmol/liter). Two subjects with glucose values (fasting <8.0 mmol/liter and 2 h postload <14.8 mmol/liter) above the cutoff points were included as well. After inclusion, fat mass and fat-free mass (FFM) were determined by underwater weighing with correction for residual lung volume (Voligraph 2000; Mijnhardt, Bunnik, The Netherlands) and calculated according to Siri (22). Extracellular water was estimated using bio-impedance (Hydra; Xitron Utilities, San Diego, CA). Maximal aerobic power (Wmax) and peak oxygen uptake (VO₂peak) were determined during an incremental exhaustive exercise test on an electronically braked bicycle ergometer (Lode, Groningen, The Netherlands). Insulin sensitivity was measured with a hyperinsulinemic euglycemic clamp (23). Insulin (1 mU/kg BW⁻¹·min⁻¹) was infused at a constant rate with glucose clamped at 4.6 mmol/liter with an iv infusion of 20% wt/vol glucose infusion. M value was calculated as the glucose infusion rate (millimoles of glucose per minute) per kilogram FFM during a steady-state of 30 min after at least 0.5 h of infusion.

**High-fat meal test**

Subjects were informed to refrain from heavy exercise like organized sports activities or heavy physical work and to consume a carbohydrate-rich dinner like pasta the day before the test. Subjects came to the laboratory by car or public transport after an overnight fast (12–14 h), during which they were only allowed to drink water. Forearm skeletal muscle was studied with the forearm model by measuring arterio-venous concentration differences across the muscle in combination with forearm blood flow measurements (24). Two catheters were inserted, one in the artery radialis and one in a retrograde direction into a deep forearm vein. The O₂-saturation in the deep venous forearm samples was less than 60%, implying that deep venous blood was drawn mainly from skeletal muscle. Blood sampling and blood flow measurements took place before and after a high-fat meal. The meal provided 2.6 MJ, which consisted of 61 energy percent (E%) from fat (of which 35.5 E% saturated, 18.8 E% monounsaturated, and 1.7 E% polyunsaturated fat), 33 E% carbohydrates and 6 E% protein. To exclude metabolism in the hand, the hand circulation on the side of the deep venous catheter was occluded (>200 mm Hg) at every measurement. Immediately after occlusion, blood flow was measured with venous occlusion plethysmography (EC5R plethysmogiph; Hokanson, Bellevue, WA). One minute after occlusion, arterial and deep venous blood samples were simultaneously drawn in EDTA syringes (1.5 mg EDTA/ml) for plasma analyses before (at −60, −30, and 0 min) and 30, 60, 90, 120, 180, and 240 min after the test meal. Blood samples were immediately centrifuged and plasma was frozen in liquid nitrogen and stored for analysis at −80°C. Plasma flow was calculated as blood sampling and blood flow measurements were taken at 30, 60, 90, 120, 180, and 240 min after the test meal. Blood samples were subsequently analyzed in duplicate.

**Biochemical analysis**

Plasma free fatty acids and glucose were analyzed using standard enzymatic techniques automated on the COBAS Fara centrifugal analyzer at 340 nm (for FFA: FFA-C test kit, Wako Chemicals, Neuss, Germany; for glucose: Roche Unikit III, Hoffman-la-Roche, Basel, Switzerland). Insulin was analyzed using a fluorometric immunometric assay (autoderma ELISA Insulin; PerkinElmer, Turku, Finland) with no cross-reactivity with proinsulin or split forms of proinsulin. IL-6 was analyzed with an ultra-sensitive ELISA kit (Quantikine HS SixPak; R&D Systems, Abingdon, UK; intraassay coefficient of variation (CV) of 3.8%). Soluble CRP (CRP-s) was analyzed on an autoanalyzer Hitachi 912 (High Sensitivity kit 1534055; Roche, Abingdon, UK; intraassay CV of 3.8%), Soluble TNF receptors R1 and R2 (soluble) were analyzed with an ELISA kit from Biosource (TNF-R1/ p55: KAC1762, intraassay CV of 7.9%; TNF-R2/p75: KAC1727, intraassay CV of 6.6%; Nivelles, Belgium). All metabolites were analyzed in duplicate (duplicate CV <10%).

**Statistical analysis**

IGT and NGT men were compared with a two-tailed Student’s t test for independent samples. IGT men before and after weight loss were compared with a two-tailed Student’s t test for paired samples. For fasting values the average of time points −60, −30, and 0 min was taken. For postprandial responses the total areas under the curve (AUC) divided by time (AUC/min) were compared. Results in the tables and text are given in mean ± sd. Data in the figures are given in mean ± sem. A P value less than 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS 10.0 for Macintosh.
Results

General

No differences were seen in age, BMI, body fat percentage, and aerobic capacity between the IGT men and the NGT men. Insulin sensitivity was not significantly different (Table 1).

Fasting metabolites and postprandial response in forearm muscle

Fasting concentrations of glucose, insulin, and free fatty acids were not different between IGT and NGT men. Postprandially, arterial glucose tended to increase more \((P = 0.10)\) in the IGT men, but the postprandial increase of arterial insulin and the postprandial decrease of arterial free fatty acid concentrations were not different between NGT and IGT (Table 2). Arterial IL-6 concentrations were not different between groups in the fasting state, nor after the meal. However, deep venous IL-6 concentrations were higher in the IGT men during fasting (IGT = 3.89 ± 1.99 vs. NGT = 2.31 ± 0.73 pg/ml, \(P = 0.03\)) and in the postprandial phase (AUC/min: IGT = 5.06 ± 3.18 vs. NGT = 2.86 ± 0.77 pg/ml, \(P = 0.05\); Fig. 1). Similar differences were found for IL-6 flux, because blood flow was not different between groups during fasting (NGT = 1.51 ± 0.47; IGT = 1.78 ± 0.60 ml/100 ml tissue\(^{-1}\)min\(^{-1}\)) or after a meal (AUC/min, NGT = 1.82 ± 0.62; IGT = 1.97 ± 0.85 ml/100 ml tissue\(^{-1}\)min\(^{-1}\)). It was found that the IL-6 release from muscle was higher in the IGT group than in the NGT group, both in the fasting state (IGT = 2.26 ± 1.89 vs. NGT = 0.87 ± 0.48 fmol/100 ml tissue\(^{-1}\)min\(^{-1}\), \(P = 0.04\)) and in the postprandial phase (AUC/min: IGT = 3.48 ± 2.63 vs. NGT = 1.37 ± 0.75 fmol/100 ml tissue\(^{-1}\)min\(^{-1}\), \(P = 0.03\); Fig. 2). The postprandial IL-6 release (AUC/min) was higher than the fasting IL-6 release (\(P < 0.05\)) in the group as a whole. Arterial CRP, TNF-R1, and TNF-R2 concentrations were not different between groups (Table 3). CRP, TNF-R1, and TNF-R2 arteriovenous differences were all less than 1% of arterial concentrations. Subsequently all fluxes were around zero, showing that CRP, TNF-R1, and TNF-R2 were not released from muscle, neither in the fasting nor in the postprandial phase.

Extrapolated estimated muscle IL-6 production

It can be calculated to what extent the release of IL-6 from muscle can contribute to systemic IL-6 levels. It has to be taken into account that these are calculated estimates, partly based on assumptions. We assumed that muscle mass, estimated as approximately 55% (25) of FFM, released IL-6 at the same rate as the forearm muscle studied here, and used an estimated half-life of 3 min (26). We estimated the IL-6 production rate of total muscle mass during fasting (mean\(_{\text{TOTAL GROUP}}\) = 0.58 ng/min, range 0.12–2.11 ng/min) and postprandially (mean\(_{\text{TOTAL GROUP}}\) = 0.90 ng/min, range 0.06–2.61 ng/min). The estimated contribution of IL-6 release from skeletal muscle to systemic IL-6, using whole body extracellular fluid estimated from bio-impedance (Hydra; Xitron Utilities), was 12% (range 2–42%) for the whole group in the fasting state. In the postprandial phase it was 11% (range 2–21%) in NGT men and highest in IGT men (25%, range 2–66%).

Effect of weight loss

Eight IGT men were willing to participate in the weight loss program. They lost on average 15.0 ± 3.4 kg of body weight (Table 1). Approximately 72% of this weight loss was owing to a reduced fat mass and 28% to a reduction in FFM. Body weight was 82.4 ± 8.3 kg in wk 8, at the end of the weight loss period, and 82.5 ± 9.4 kg in wk 10, just before repeating the measurements, indicating that subjects were in energy balance during the measurement period. Weight loss improved insulin sensitivity (Table 1), reduced fasting arterial glucose, insulin, and free fatty acid concentrations and reduced postprandial hyperglycemia (−8%) and hyperinsulinemia (−41%) (Table 2). No change was seen in aerobic capacity (Table 1).

After weight loss (WL), no significant change was observed in fasting arterial IL-6 concentrations (Table 3) or fasting IL-6 release from muscle (IGT\(_{\text{PRE WL}}\): 2.22 ± 1.86 vs. IGT\(_{\text{AFTER WL}}\): 1.40 ± 1.32 fmol/100 ml tissue\(^{-1}\)min\(^{-1}\); Fig. 1; \(P = 0.24\)), but postprandial IL-6 release had decreased (IGT\(_{\text{PRE WL}}\): 2.99 ± 2.58 vs. IGT\(_{\text{AFTER WL}}\): 1.45 ± 1.33 fmol/100 ml tissue\(^{-1}\)min\(^{-1}\), \(P = 0.04\)) after weight loss (Fig. 2). Weight

### TABLE 1. General and metabolic characteristics of the obese men

<table>
<thead>
<tr>
<th></th>
<th>NGT (n = 9)</th>
<th>IGT (n = 11)</th>
<th>IGT Before WL (n = 8)</th>
<th>IGT After WL (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55.9 ± 7.2</td>
<td>55.5 ± 7.9</td>
<td>56.1 ± 8.4</td>
<td>80.2 ± 7.6*a</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>107.0 ± 19.2</td>
<td>95.9 ± 7.8</td>
<td>95.2 ± 7.6</td>
<td>80.2 ± 6.5*a</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>69.5 ± 10.8</td>
<td>64.8 ± 5.0</td>
<td>63.2 ± 3.6</td>
<td>58.9 ± 4.2*b</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>34.6 ± 4.8</td>
<td>32.1 ± 2.3</td>
<td>32.2 ± 4.4</td>
<td>27.5 ± 1.5*a</td>
</tr>
<tr>
<td>Body fat %</td>
<td>34.6 ± 6.0</td>
<td>32.5 ± 3.0</td>
<td>33.6 ± 2.1</td>
<td>26.3 ± 3.6*b</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>1.02 ± 0.05</td>
<td>1.03 ± 0.04</td>
<td>1.04 ± 0.03</td>
<td>0.99 ± 0.03*a</td>
</tr>
<tr>
<td>VO(_2) peak (ml O(_2)/kg FFM(^{-1})min(^{-1}))</td>
<td>39.7 ± 6.0</td>
<td>41.0 ± 4.8</td>
<td>39.7 ± 4.3</td>
<td>40.9 ± 7.2</td>
</tr>
<tr>
<td>Glucose, fasting (capillary, mmol/liter)</td>
<td>5.7 ± 0.6</td>
<td>6.5 ± 0.9b</td>
<td>6.7 ± 1.0</td>
<td>n.d.</td>
</tr>
<tr>
<td>Glucose, 2 h after 75-g glucose load (capillary, mmol/liter) (mg/dl)</td>
<td>6.7 ± 1.2</td>
<td>11.9 ± 2.0c</td>
<td>12.7 ± 2.0</td>
<td>n.d.</td>
</tr>
<tr>
<td>Insulin sensitivity (M value, μmol/kg FFM(^{-1})min(^{-1}))</td>
<td>32.4 ± 14.3</td>
<td>24.5 ± 10.8</td>
<td>23.3 ± 9.4</td>
<td>39.2 ± 11.7*p</td>
</tr>
</tbody>
</table>

\(a\) \(P < 0.01\) IGT before weight loss vs. after weight loss; paired test with \(n = 8\).

\(b\) \(P < 0.05\) NGT vs. IGT.

\(c\) \(P < 0.01\) NGT vs. IGT.
loss also decreased the arterial CRP level (−45%, P = 0.004, Table 3), whereas the TNF-R1 receptor showed a trend for a lower concentration (−7%, P = 0.06, Table 3). No correlations between M value, body weight loss, and IL-6 release were found.

**Discussion**

A major finding of the present study is that the cytokine IL-6 was released from skeletal muscle of obese IGT and obese NGT men during fasting and after a high-fat meal. Interestingly, the IL-6 release from forearm muscle was higher in obese men with IGT compared with obese men with NGT. Furthermore, in IGT men, the IL-6 release from muscle after a high-fat meal was reduced after weight loss, in concert with improvements in insulin sensitivity and glucose tolerance.

It has been reported before that the venous IL-6 concentration increases after a meal, especially after a high-fat meal (20, 21). This is the first report describing IL-6 release in the postprandial phase by skeletal muscle. In the present study, it was calculated that the estimated total muscle mass would produce 7 vs. 16% of the systemic IL-6 during fasting and 11 vs. 25% in the postprandial phase for NGT and IGT subjects, respectively. Mohamed-Ali et al. (27) previously reported that the estimated production rate of whole body adipose tissue was 1.41 ng/min (range 0.22–2.67 ng/min), which was in the same range as the values we found for muscle in the postprandial phase in IGT men before weight loss (1.17 ng/min, range 0.15–2.61 ng/min). Thus, both adipose tissue and skeletal muscle contribute to circulating IL-6 concentrations. The question remains whether the IL-6 is produced by myocytes or by other cell types present in muscle, because it has recently been found that the IL-6 release from adipose tissue derives 90% from nonadipocytes (28). Although it is known that IL-6 can be released by muscle fibers themselves (13, 29), the contribution of other cell types such as monocytes/macrophages, endothelial cells, fibroblasts, and smooth muscle cells cannot be excluded. The contribution of other tissues in the forearm, like adipose tissue, cannot be entirely excluded either, although the deep venous plasma was mainly drawn from muscle, as confirmed by an O2-saturation less than 60%.

It is still unclear what may trigger IL-6 release from muscle. We cannot even exclude that the experimental conditions per se may have had an effect on IL-6 release from muscle, because we did not include a control group for the meal-effect. Nevertheless, it is likely that the meal per se evoked an

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**TABLE 2.** Fasting and postprandial arterial concentrations of glucose, insulin, and free fatty acids in men with NGT, IGT, and IGT after weight loss

<table>
<thead>
<tr>
<th>Glucose, fasting (mmol/liter)</th>
<th>Postprandial AUC</th>
<th>Insulin, fasting (mU/liter)</th>
<th>Postprandial AUC</th>
<th>Free fatty acid, fasting (μmol/liter)</th>
<th>Postprandial AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT (n = 9)</td>
<td>IGT (n = 11)</td>
<td>Before WL (n = 8)</td>
<td>After WL (n = 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.8 ± 0.3</td>
<td>6.0 ± 0.5</td>
<td>5.9 ± 0.6</td>
<td>5.3 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.57 ± 0.47</td>
<td>7.08 ± 0.65*</td>
<td>7.07 ± 0.75</td>
<td>6.47 ± 0.33*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.0 ± 12.7</td>
<td>14.4 ± 3.8</td>
<td>14.3 ± 4.5</td>
<td>6.5 ± 3.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.5 ± 13.7</td>
<td>38.2 ± 14.7</td>
<td>34.5 ± 11.5</td>
<td>20.9 ± 9.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>505 ± 166</td>
<td>675 ± 184</td>
<td>697 ± 201</td>
<td>556 ± 102*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>359 ± 70</td>
<td>440 ± 148</td>
<td>473 ± 163</td>
<td>360 ± 92*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD. Postprandial AUC as mean per minute (AUC/min).

*P < 0.05 IGT before weight loss vs. after weight loss; paired test with n = 8.

"P < 0.10 difference between NGT and IGT.

"P < 0.01 IGT before weight loss vs. after weight loss; paired test with n = 8.
effect on IL-6 release, because the postprandial IL-6 release (AUC/min) was higher than the fasting IL-6 release \((P < 0.05)\) in the group as a whole. Several factors may provoke IL-6 release from muscle. In the first place, the production of cytokines in skeletal muscle, like IL-6, may be stimulated by oxidative stress \((30)\). One of the factors that may cause oxidative stress in the postprandial period is impaired substrate handling \((31)\), as described in IGT and DM2 \((24, 32)\). Impairments in lipid \((33)\) and glucose \((34)\) handling may both lead to oxidative stress. In the second place, impairments in lipid metabolism, like a reduced oxidation of plasma-derived fatty acids \((24, 32)\) in DM2 subjects may lead to the accumulation of interstitial or cytosolic free fatty acids. Especially saturated fatty acids like palmitate can directly stimulate the production of IL-6 in myocytes from DM2 patients \((13)\), when present in abundance. So, impairments in substrate handling, as found in IGT and DM2, may lead to the production of free radicals, and/or to an increment of local concentrations of saturated free fatty acids. Each of these may stimulate the production of IL-6 in the postprandial phase. The physiological significance of IL-6 release from muscle is still unclear. Pedersen \textit{et al.} \((35)\) suggested that IL-6 may be an interorgan signaling molecule during exercise, reporting a signal from skeletal muscle to the liver to indicate the use of glycogen. However, this is not likely to be the case after meal intake.

What may be the effect of the cytokines that are produced on skeletal muscle metabolism? It has been shown that systemic IL-6 infusion, resulting in high arterial IL-6 concentrations \((-150 \text{ pg/ml})\), stimulates lipolysis and fatty acid oxidation in humans in rest \((36)\), although it is not known whether similar effects will be found in the physiological range. However, in adipose tissue, it has been shown that interstitial IL-6 concentrations may be up to approximately 100 times as high as plasma values \((37)\). Likewise, high interstitial amounts of IL-6 may affect fatty acid metabolism in an auto- or paracrine manner. On the other hand, it has been reported that IL-6 infusion did not affect glucose uptake or oxidation, and \textit{in vitro} and \textit{in vivo} studies show no effect of IL-6 on insulin action in skeletal muscle \((12-14)\). However, IL-6 may induce tissue insulin resistance in other organs, \textit{e.g.} in liver \((11, 12)\), thus contributing to the further progression of IGT to DM2.

After weight loss, arterial IL-6 concentrations had not changed, but the postprandial release of IL-6 from muscle was decreased \((-52\%, \ P = 0.04)\). This improvement in IL-6 release after weight loss may have been a consequence of the reduction in body weight, the improvement of glucose tolerance and/or the increase in insulin sensitivity. This supports the concept that the postprandial increase in IL-6 production may have been triggered by disturbances in glucose and/or fat metabolism found in obese IGT men.

The lack of differences between NGT and IGT subjects in arterial concentrations of IL-6, CRP, TNF-R1, and TNF-R2 is in accordance with some \((5, 38)\), but not all studies \((3)\) and may be explained by the fact that the observed groups are equally obese and only slightly different in insulin resistance.

In conclusion, we observed IL-6 release from forearm muscle in obese NGT and obese IGT men, both during fasting and after a meal. IL-6 release was significantly higher in IGT men during the postprandial phase when compared with obese NGT men. In these IGT men, the postprandial IL-6 release decreased after body weight loss, reaching levels that were found in the obese, NGT controls. We suggest that the high-fat meal may be an important metabolic stressor, evoking IL-6 release from skeletal muscle, due to the impairment in substrate handling in IGT men and that the IL-6 production may rather be a consequence than a cause of the obese, insulin-resistant and/or IGT state. Further studies have to provide more information on the mechanisms that are responsible for the increased IL-6 production by muscle, and whether the production of IL-6 in muscle may lead to a further increase in insulin resistance, contributing to the progression of IGT to DM2.

### Acknowledgments

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### Table 3. Fasting arterial concentrations of IL-6, CRP, and TNF-\(\alpha\) receptors in men with NGT, IGT, and IGT after weight loss

<table>
<thead>
<tr>
<th></th>
<th>NGT ((n = 9))</th>
<th>IGT ((n = 11))</th>
<th>(P) value</th>
<th>IGT before WL ((n = 8))</th>
<th>IGT after WL ((n = 8))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>1.33 ± 0.57</td>
<td>1.47 ± 0.42</td>
<td>0.57</td>
<td>1.58 ± 0.40</td>
<td>1.41 ± 0.41</td>
<td>0.23</td>
</tr>
<tr>
<td>CRP-(s)</td>
<td>2.21 ± 1.71</td>
<td>3.46 ± 1.90</td>
<td>0.15</td>
<td>4.21 ± 1.75</td>
<td>2.09 ± 1.15</td>
<td>0.004</td>
</tr>
<tr>
<td>TNF-R1</td>
<td>1.52 ± 0.22</td>
<td>1.45 ± 0.23</td>
<td>0.55</td>
<td>1.45 ± 0.27</td>
<td>1.35 ± 0.28</td>
<td>0.06</td>
</tr>
<tr>
<td>TNF-R2</td>
<td>3.27 ± 0.89</td>
<td>3.65 ± 0.87</td>
<td>0.42</td>
<td>3.59 ± 0.67</td>
<td>3.65 ± 2.01</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Mean ± SD. IL-6 is given in picograms per milliliter, CRP-s in milligrams per liter, and TNF-R1 and TNF-R2 are given in nanograms per milliliter.
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