

Adipose and Liver Expression of Interleukin (IL)-1 Family Members in Morbid Obesity and Effects of Weight Loss

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Morbid obesity is associated with a state of chronic inflammation. Interleukin-1 family (IL-1F) cytokine members are produced by human adipose tissue in obesity. Whereas certain IL-1F members such as IL-1 β or IL-18 are potently proinflammatory, others such as IL-1 receptor antagonist (IL-1Ra) or IL-37 (formerly IL-1F7) are antiinflammatory. The NLRP3 inflammasome plays a key role in the processing of bioactive IL-1 β and IL-18. We investigated the effect of excessive weight loss on subcutaneous adipose tissue and liver expression of IL-1 α , IL-1 β , IL-18, IL-1Ra, IL-37 and NLRP3. Twenty-one severely obese patients undergoing laparoscopic adjustable gastric banding surgery were studied. Tissue samples were collected before and 6 months after laparoscopic adjustable gastric banding surgery. mRNA expression of all studied IL-1F members, but especially of IL-37, was much higher in subcutaneous/visceral adipose tissue compared with their liver expression. Subcutaneous adipose tissue mRNA expression of IL-1 β decreased significantly after extensive weight loss; expression of IL-18 and IL-1Ra did not change, whereas IL-37 expression increased. Weight loss led to a significant reduction in liver IL-1 β , IL-18 and IL-1Ra expression, whereas hepatic IL-37 mRNA expression remained stable. Adipose/liver NLRP3 inflammasome and IL-1 α expression were not affected by weight loss. Tissue expression of IL-1 β , IL-18 and IL-37 were significantly higher in subcutaneous/visceral adipose tissue compared with the liver. In conclusion, expression of IL-1F members is more pronounced in adipose compared with liver tissue in patients with severe obesity. Excessive weight loss changes the adipose and liver expression profile of IL-1F members toward a more antiinflammatory direction.

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INTRODUCTION

Obesity is characterized by a state of low-grade inflammation associated with increased cytokine production. Adipose tissue, which is infiltrated by monocytes/macrophages and other inflammatory cells in morbid obesity, secretes numerous soluble mediators, including adipocytokines such as adiponectin or leptin and many classical cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-6 and IL-1 family (IL-1F) members (1).

IL-1 β is among the first identified cytokines and exerts strong proinflammatory functions (2,3). The potent proin-

flammatory properties of IL-1 β are tightly regulated by expression, processing, secretion and antagonism by natural inhibitors such as IL-1 receptor antagonist (IL-1Ra) (2). Concentrations of IL-1 β are elevated in the circulation of patients with severe obesity and also in pancreatic cells during the progression from obesity to type 2 diabetes (4). IL-1 β maturation is controlled by a multiprotein complex called inflammasome (NLRP3) (5). The NLRP3 inflammasome contains the adaptor protein apoptosis-associated specklike protein (ASC), NLRP3 and caspase-1, a proinflammatory enzyme that cleaves pro-IL-1 β , thereby leading to the bioac-

tive form. The NLRP3 inflammasome has been associated with the pathogenesis of type 2 diabetes (6). Stienstra *et al.* (7) recently demonstrated that caspase-1 and IL-1 β activity increase in adipose tissue of dietary as well as genetically obese mice. Importantly, the authors demonstrated that mice defective in caspase-1 were more insulin sensitive and that treatment of obese mice with a caspase-1 inhibitor improved insulin sensitivity *in vivo* (7). IL-18 is another proinflammatory IL-1F member (8). Similar to IL-1 β , IL-18 is first synthesized as an active precursor (pro-IL-18) and requires caspase-1 for processing and activation. IL-18 is also upregulated in adipose tissue of obese mice and humans (9–11).

Several IL-1F members have antiinflammatory functions. IL-1Ra, which binds to IL-1 receptors thereby preventing IL-1 signal transduction, is markedly upregulated in the serum of obese

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patients, correlates with body mass index and insulin resistance and is overexpressed in the white adipose tissue of obese humans (12,13). IL-1F7 is a unique antiinflammatory cytokine similar in function to IL-10. IL-1F7 (now also known as IL-37) potentially suppresses the production of proinflammatory cytokines by macrophages, and IL-37 transgenic mice are protected from lipopolysaccharide-induced septic shock (14). IL-37 recruits an accessory receptor chain with inhibitory properties and likely binds to the IL-18R α chain (15). The antiinflammatory properties of IL-37 depend on the activation of Smad3 (14).

IL-1F members have been associated with development of insulin resistance and type 2 diabetes, and neutralization of IL-1 β improves metabolic parameters both in preclinical and clinical trials of type 2 diabetes (4,16,17). Because the contribution of adipose versus liver tissue as sources of IL-1F members in obesity and obesity-associated diseases remains unclear, we studied the effects of weight loss achieved after bariatric surgery on the expression of IL-1F members in these tissues.

MATERIAL AND METHODS

Selection of Patients

A total of 21 (7 male, 14 female) severely obese patients (body mass index [BMI] <40 kg/m²) were enrolled in the study. Type 2 diabetes mellitus, as defined by a fasting glucose of >126 mg/dL, was diagnosed in one patient (4.8%) before and none of the patients after weight loss. Alternative causes for chronic liver diseases such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease and α 1-antitrypsin deficiency were excluded in all subjects. Current and past alcohol intake was <20 g/wk, and all patients were negative for hepatitis B and C. Patients were placed with a laparoscopic adjustable gastric banding (LAGB) device. All patients provided written informed consent. The study protocol was approved by the ethics committee of the Medical University Innsbruck. Some of

the patients were the subject of earlier reports (18–20).

An index liver biopsy and visceral/subcutaneous tissue samples were collected under laparoscopic guidance at the time of band placement. Six months later, we performed an ultrasound-guided follow-up liver biopsy and collected a follow-up subcutaneous adipose tissue probe. Blood samples were drawn in the fasting state at the time of index and follow-up biopsies. Routine clinical parameters were measured by automated techniques, and specimens for cytokine and mRNA analysis were stored at –80°C until further analysis. Baseline characteristics of study subjects are summarized in Table 1.

Quantification of Tissue Cytokine Expression

The steady-state tissue mRNA levels of IL-1 α , IL-1 β , IL-18, IL-1Ra, IL-1F7 and NLRP3 were assessed by semi-quantitative real-time polymerase chain reaction (PCR) as described previously (18). Total RNA was extracted by homogenization of tissue samples in Trizol Reagent (Invitrogen, Paisley, Scotland) according to the manufacturer's instructions. RNA (1 μ L) was reverse-transcribed using moloney murine leukemia virus (M-MLV) reverse transcriptase (Invitrogen). Quantitative PCRs (25 μ L) were run in duplicates on a Stratagene Mx3000 bioanalyzer (Stratagene, Amsterdam, the Netherlands) using SYBR Green reagents (Eurogentec, Seraign, Belgium). Expression levels were calculated using the standard-curve method. One cDNA, derived from stimulated primary leukocytes, served as a standard for all measurements. The abundance of each mRNA was expressed as ratio to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA expression. GAPDH ratios were confirmed by normalization to actin- β (data not shown). The following primer sequences were used: IL-1 α , forward: 5'-AGA AGA GAC GGT TGA GTT TAA GCC AAT CCA-3'; IL-1 α , reverse: 5'-CTC AGG AAG CTA AAA GGT GCT GAC CTA-3'. IL-1 β , forward:

5'-TGT TGA AAG ATG ATA AGC CCA CTC T-3'; IL-1 β , reverse: 5'-CAA ATC GCT TTT CCA TCT TCT TC-3'; IL-18, forward: 5'-TGG CTG CTG AAC CAG TAG AAG AC-3'; IL-18, reverse: 5'-GCC GAT TTC CTT GGT CAA TGA AGA G-3'; NLRP3, forward: 5'-GAA GTG GGG TTC AGA TAA TGC ACG TG-3'; NLRP3, reverse: 5'-CGA AAG GTA CTC CAG TAA ACC CAT CC-3'; IL-1Ra, forward: 5'-CAT TGA GCC TCA TGC TCT GTT CTT-3' G; IL-1Ra, reverse: 5'-CTT TCT GTT CTC GCT CAG GTC AGT GA-3'; IL-1F7, forward: 5'-CAG CCT CTG CGG AGA AAG GAA GT-3'; IL-1F7, reverse: 5'-GTT TCT CCT TCT TCA GCT GAA GGG ATG GAT-3'.

Statistical Analysis

The results are expressed as means \pm SD. The degree of association between variables was calculated using Spearman's nonparametric correlation. Differences between the baseline and 6-month values were determined using Student paired *t* tests for normally distributed variables, and Wilcoxon signed-rank test was used for not-normally-distributed variables. All statistical tests were performed with PASW statistics 17.0 (SPSS Inc., Chicago, IL, USA) and independently confirmed by GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA, USA). *P* values were two-tailed and a significance level of 5% was used throughout.

RESULTS

Changes in Anthropomorphic, Biochemical and Metabolic Parameters

Six months after LAGB surgery, we observed a significant weight loss ranging from 18.5 to 50.5 kg, corresponding to a mean weight loss of 24.7 \pm 8.1 kg. Patient characteristics are featured in Table 1. Surgery-induced weight loss was associated with a significant improvement in laboratory parameters, such as alanine aminotransferase, γ -glutamyl transferase (GGT) and C-reactive protein (CRP) levels (see Table 1). Moreover, weight loss resulted in a significant improvement of

Table 1. Patient characteristics and metabolic and inflammatory markers before and 6 months after LAGB.

Measurement	Index	After weight loss	Wilcoxon <i>P</i> value
Number and sex of subjects	21 (7 M/14 F)		
Age of subjects (years) (range)	36.9 (19–66)		
BMI (kg/m ²) (range)	43.1 ± 3.9 (37.2 – 50.5)	34.9 ± 4.4 (26.4 – 42.4)	<0.001
Weight loss (kg) (range)		24.7 ± 8.1 (18.5–50.5)	
Aspartate amino transferase (units/L) (range)	30.7 ± 13.9 (20–83)	25.0 ± 6.5 (15–44)	0.07
Alanine amino transferase (units/L) (range)	36.8 ± 29.9 (15–121)	23.7 ± 10.4 (8–63)	<0.05
γ-Glutamyl transferase (units/L) (range)	34.4 ± 21.3 (18–111)	23.9 ± 10.4 (12–57)	<0.01
Fasting glucose (mg/dL) ^a (range)	102 ± 16 (87–158)	89 ± 8 (69–106)	<0.001
Fasting insulin (μU/mL) ^b (range)	21.4 ± 16.2 (6.3–71.5)	11.5 ± 8.0 (3.4–35.4)	<0.01
HOMA index (range)	5.6 ± 4.7 (1.4–18)	2.6 ± 2.0 (0.8–9.1)	<0.01
Glycated hemoglobin (%) (range)	5.7 ± 0.8 (5.1–6.3)	5.6 ± 0.7 (5.2–5.9)	NS ^c
Leukocytes (10 ³ /μL) (range)	7.5 ± 1.9 (5.0–12.2)	6.3 ± 1.4 (4.1–8.8)	<0.01
C-reactive protein (μg/dL) (range)	1.1 ± 0.7 (0.3–3.8)	0.6 ± 0.3 (0.1–1.4)	<0.05

Blood for all studies was drawn with subjects in the fasting state. Data are given as means ± SD. Differences 6 months after bariatric surgery were analyzed by the Wilcoxon signed-rank test.

^aTo convert values to millimoles per liter, multiply by 0.05549.

^bTo convert values to picomoles per liter, multiply by 7.175.

^cNot significant.

biochemical markers for glucose homeostasis such as fasting glucose, insulin levels and homeostasis model assessment (HOMA) index (see Table 1).

Changes in Hepatic IL-1F Cytokine Member Expression

Changes in hepatic mRNA expression of IL-1F members, before and 6 months after weight loss, were determined by quantitative real-time PCR. Hepatic IL-1β mRNA expression decreased significantly 6 months after weight loss (Figure 1B; *P* < 0.01). A 2.1-fold decrease of liver IL-18 expression was seen in follow-up compared with index liver biopsies (Figure 1C, *P* < 0.001). No difference was found between baseline and follow-up IL-1α expression (Figure 1A). Hepatic NLRP3 expression also remained unchanged (Figure 1D). Weight loss was associated with a 2.8-fold reduction in hepatic IL-1Ra mRNA expression (Figure 2A, *P* < 0.01). No significant alterations were observed in liver IL-37 expression (Figure 2B).

Changes in Subcutaneous Adipose Tissue IL-1F Cytokine Member Expression

Next, we determined IL-1F members in subcutaneous adipose tissue, again

comparing baseline and follow-up tissue samples. Regarding IL-1β, we noticed a 3.5-fold decline of adipose tissue mRNA expression (see Figure 1B, *P* < 0.01). IL-1α was hardly detectable in subcutaneous adipose tissue samples (9 patients before weight loss, 11 patients after weight loss, see Figure 1A). As depicted in Figure 1C and D, we did not observe significant changes regarding adipose tissue expression of IL-18 and NLRP3. In the same way, subcutaneous IL-1Ra expression remained unaffected (see Figure 2A). Interestingly, weight loss was associated with a significant 3.8-fold increase in adipose IL-37 expression (see Figure 2B, *P* < 0.01).

We next studied whether differences existed when comparing liver and subcutaneous/visceral adipose tissue IL-1F cytokine expression. Expression of all assessed IL-1F cytokine members was much more abundant in visceral compared with subcutaneous adipose tissue (for details, see Figures 1 and 2). Furthermore, expression of IL-1β, IL-18, IL-1Ra and IL-37 again was significantly higher in subcutaneous tissue compared with their liver expression patterns (see Figures 1 and 2). NLRP3 inflammasome expression was similar in subcutaneous

and visceral adipose tissue. Therefore, expression of IL-1F members was generally highest in visceral adipose tissue and lowest in the liver, suggesting that the adipose tissue is the major source for various IL-1F members in obesity and/or obesity-related inflammation.

Correlations of Liver and Subcutaneous IL-1F Members with Demographic, Biochemical and Inflammatory Parameters

Significant positive associations were observed between subcutaneous IL-1β and BMI ($r_s = 0.426$, *P* = 0.008), insulin ($r_s = 0.292$, *P* < 0.05) and HOMA index ($r_s = 0.313$, *P* < 0.05). In contrast, significant negative correlations were found between IL-37 and BMI ($r_s = -0.341$, *P* < 0.05), serum insulin ($r_s = -0.435$, *P* = 0.006) and HOMA index ($r_s = -0.479$, *P* = 0.002). For further details, see Table 2.

DISCUSSION

We demonstrate that (i) in severe human obesity, subcutaneous adipose tissue, especially visceral adipose tissue, is a much more prominent source of IL-1F members compared with liver tissue; (ii) weight loss results in a decrease of IL-1β accompanied by improved insulin sensi-

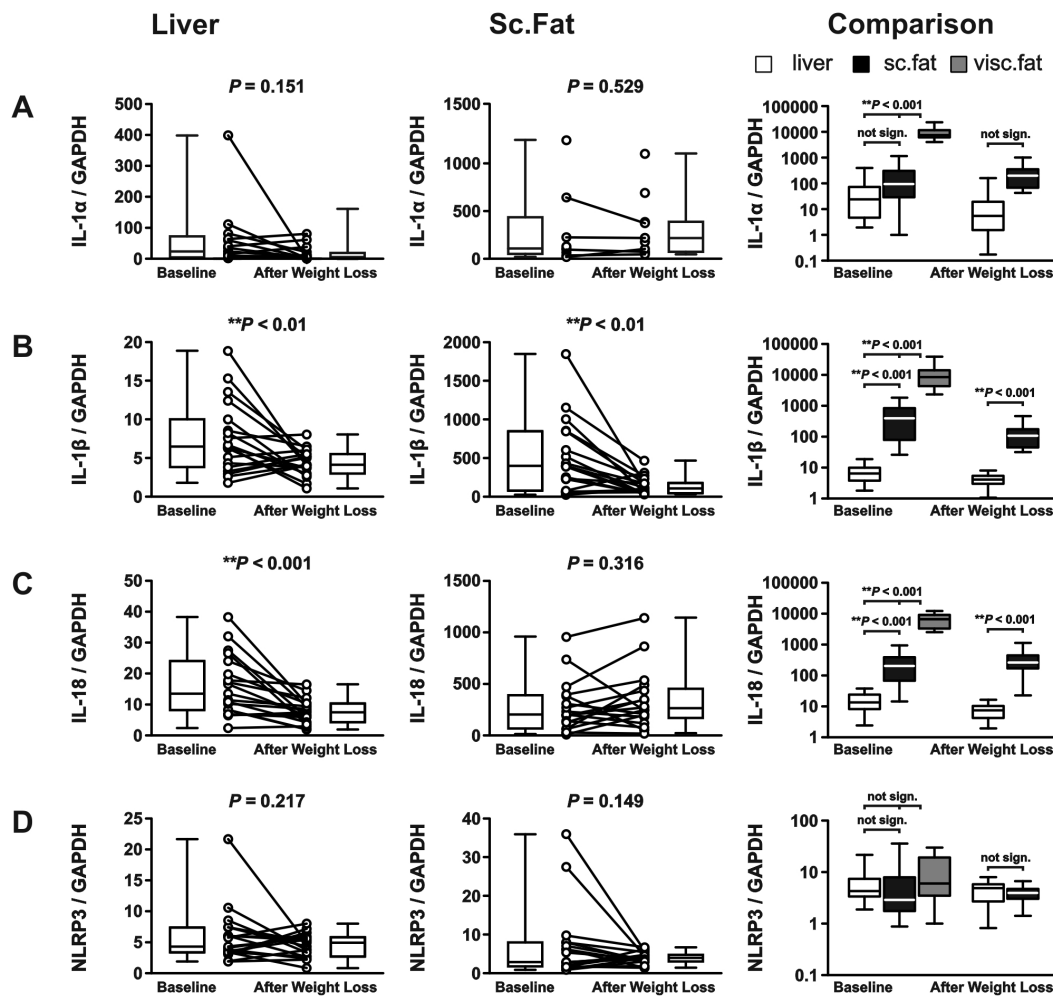


Figure 1. Changes in proinflammatory IL-1F cytokine member mRNA levels in hepatic and subcutaneous (Sc.) adipose tissue before and after weight loss induced by bariatric surgery. (A) IL-1 α mRNA expression is barely detectable in both liver tissue and subcutaneous adipose tissue. Highest IL-1 α mRNA levels are observed in the visceral (visc.) adipose tissue. (B) A significant reduction in both liver and subcutaneous fat IL-1 β expression in individual study subjects after weight loss. The relative abundance of IL-1 β mRNA is higher in subcutaneous adipose than in the liver and highest in the visceral fat compartment. (C) IL-18 mRNA expression in liver and subcutaneous fat before and after LAGB. Liver IL-18 mRNA levels decline significantly after weight loss. No significant alterations are observed in subcutaneous adipose tissue. IL-18 expression is most pronounced in visceral adipose tissue. (D) NLRP3 expression before and after weight loss. No significant weight loss-related or tissue-specific differences in NLRP3 mRNA expression are identified. Box plots represent values as median (**bold horizontal line**), 75% confidence interval (**box**) and minimum and maximum values (**whiskers**). sign., significant.

tivity; and (iii) weight loss leads to an increase in the adipose expression of certain antiinflammatory IL-1F members such as IL-37. Well-described improvements in systemic inflammatory parameters after weight loss may therefore be explained partly by the changes described here in cytokine expression profiles.

Expression of IL-1F members in adipose/liver tissue before and after weight loss has not been studied so far. Most studies in the past concentrated on

the assessment of serum levels of IL-1 β and IL-1Ra after weight loss. We recently demonstrated in a similar cohort of patients that expression of other proinflammatory cytokines such as IL-6 and TNF- α also decreases in both adipose and liver tissue after weight loss (18). Clement *et al.* (21) studied gene expression profiles of subcutaneous white adipose tissue from 29 obese subjects during a low-calorie diet using cDNA microarrays and quantitative RT-PCR. Importantly, studied genes were

expressed mostly in the stromavascular fraction of adipose tissue, which contains monocytes/macrophages. The only identified and studied IL-1F member had been IL-1Ra, although available data revealed different results. A 28-day diet with an average weight loss of 6 kg was associated with an increase of mRNA adipose tissue expression of both IL-10 and IL-1Ra (21). Meier *et al.* (22) showed that obesity is associated with a 6.5-fold increase in circulating IL-1Ra levels. In their study, weight

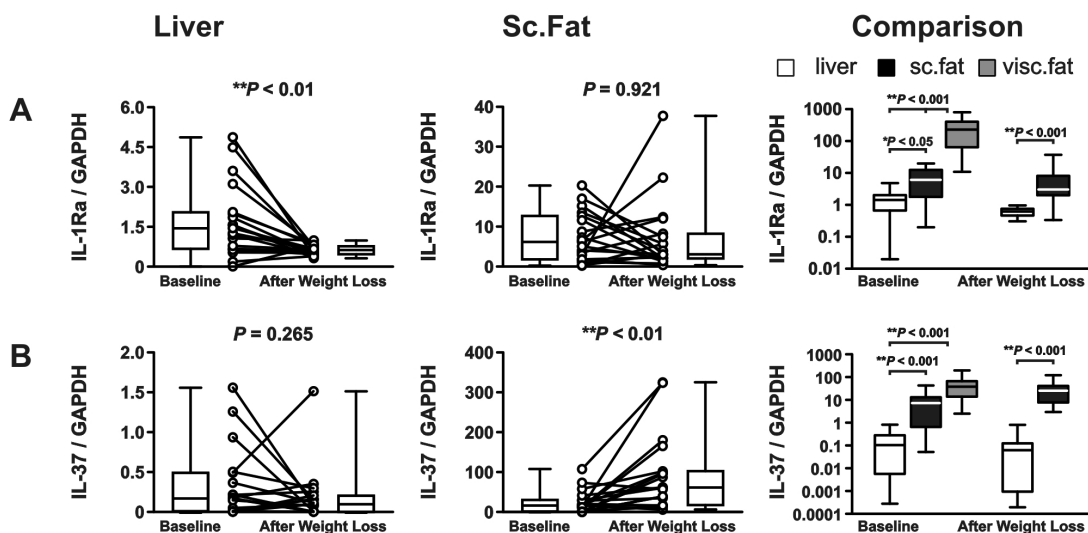


Figure 2. Changes in antiinflammatory IL-1F cytokine member mRNA levels in hepatic and subcutaneous (Sc.) adipose tissue before and after weight loss induced by bariatric surgery. (A) Expression of IL-1 receptor antagonist (IL-1Ra) in liver and adipose tissue before and after weight loss. Hepatic IL-1Ra mRNA concentrations significantly fall after weight loss. No such difference is seen in subcutaneous adipose tissue. IL-1Ra mRNA expression is significantly higher in subcutaneous fat and highest in visceral (visc.) adipose tissue compared with hepatic concentrations. (B) Expression analysis of the antiinflammatory cytokine IL-37 in liver and subcutaneous adipose tissue. Although weight loss does not influence hepatic IL-37 expression, we observe a significant increase in subcutaneous adipose tissue IL-37. The difference between subcutaneous and visceral adipose tissue IL-37 expression does not reach statistical significance. Box plots represent values as median (*bold horizontal line*), 75% confidence interval (*box*) and minimum and maximum values (*whiskers*).

loss induced by gastric bypass surgery induced a modest although significant decrease in circulating IL-1Ra levels after 6 months. However, compared with lean controls, circulating IL-1Ra levels were still 4.5-fold higher after weight loss and marked individual differences in the response of IL-1Ra reduction were observed (22). In contrast, we observed in our patients no significant increase in IL-1Ra adipose tissue expression despite an extensive weight loss of 26.1 ± 7.8 kg. Persistent increased IL-1Ra adipose tissue expression, as observed in our study, might therefore reflect a strategy to restore metabolic as well as inflammatory homeostasis. Interestingly, we observed an increase in adipose tissue expression of another antiinflammatory IL-1F member, namely IL-37. Changes in the expression pattern of IL-37 resemble those observed for adiponectin (15), and interestingly, expression of this antiinflammatory IL-1F member after weight loss was almost 500 times higher in adipose versus liver tissue. A weakness of our study is the fact that we isolated total RNA from whole adipose

Table 2. Correlations of liver and subcutaneous fat IL-1 β , IL-18, IL-1Ra and IL-37 with BMI, markers of insulin resistance, liver function parameters and markers of systemic inflammation.

	r_s^a	P
Liver cytokines		
IL-1 β with BMI	0.314	<0.05
IL-18 with BMI	0.318	<0.05
IL-18 with CRP	0.343	<0.05
IL-1Ra with BMI	0.386	<0.05
IL-37 with BMI	0.304	<0.05
IL-37 with GGT	-0.340	<0.05
Subcutaneous fat cytokines		
IL-1 β with BMI	0.426	0.008
IL-1 β with insulin	0.292	<0.05
IL-1 β with HOMA	0.313	<0.05
IL-1Ra with GGT	0.359	<0.05
IL-1Ra with alkaline phosphatase	0.462	0.003
IL-1Ra with insulin	0.503	<0.001
IL-1Ra with HOMA	0.456	0.004
IL-37 with BMI	-0.341	<0.05
IL-37 with insulin	-0.435	0.006
IL-37 with HOMA	-0.479	0.002

Blood for all studies was drawn in the fasting state, centrifuged and stored at -80°C until measurements.

^aSpearman correlation coefficient.

tissue samples not separating adipocytes from the stromavascular fraction, although it is likely that studied IL-1F members are derived from the monocyte/macrophage adipose tissue fraction.

IL-1 β recently regained a lot of interest, since this proinflammatory cytokine is involved in the pathophysiology of islet inflammation in type 2 diabetes, and its neutralization by either IL-1Ra or neutralizing antibodies demonstrated clinical benefit (4,17,23). In a diet-induced obesity model (XOMA 052), a neutralizing anti-IL-1 β antibody was administered to mice fed either a normal or high-fat diet. This therapy improved insulin sensitivity and led to β -cell sparing (16). IL-1 β along with IL-6 concentrations predict risk for type 2 diabetes in humans better than either cytokine alone (24). It was recently shown that elevated IL-1Ra levels exist over >10 years and there is an accelerated increase during the last 6 years before type 2 diabetes diagnosis (25). It was also postulated that increased IL-18 concentrations observed in patients with type 2 diabetes might reflect a role in the regulation of insulin resistance (26,27), although IL-18 expression in our patients only decreased in the liver but not in the adipose tissue. Tissue expression of the NLRP3 inflammasome, which drives IL-1 β and IL-18 maturation/secretion, did not change after weight loss; however, posttranscriptional modifications of this important inflammasome cannot be ruled out and may be even more relevant. Unfortunately, we were not able to determine adipose tissue caspase-1 activity. Only recently, Stienstra *et al.* (7) convincingly demonstrated that caspase-1 activity is significantly increased in the adipose tissue of dietary and genetically obese mice. Increased caspase-1 activity was associated with significantly elevated IL-1 β and IL-18 protein levels in adipose tissue. Importantly, both genetic deletion as well as pharmacological inhibition of caspase-1 improved insulin sensitivity in obese mice (7).

Adipose tissue inflammation accompanied by elevated systemic inflammatory parameters is a common principle in severe obesity, although certain patients

may have a less inflammatory phenotype. We convincingly demonstrate that excessive weight loss significantly affects expression of IL-1F members in adipose and liver tissue, thereby potentially contributing to the improvement of insulin resistance and inflammation in our patients. Changes after moderate weight loss may be somewhat different (21). Targeting proinflammatory cytokines might reveal an attractive treatment concept in obesity-related inflammatory disorders.

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DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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