SciMedCentral

JSM Gastroenterology and Hepatology

Research Article

Inflammation-Related Proteins Are Differently Associated With Visceral Adipose Tissue, Liver Fat, and Pancreatic Fat

Lars Lind[1], Ulf Risérus[2], Joel Kullberg[3,4], Håkan Ahlström[3,4], Jan W Eriksson[1], and Jan Oscarsson[5]*

[1]Department of Medical Sciences, Uppsala University, Sweden
[2]Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University, Sweden
[3]Antaros Medical AB, Gothenburg, Sweden
[4]Department of Surgical Sciences, Radiology, Uppsala University, Sweden
[5]Biopharmaceuticals R&D, Late-stage Development, Cardiovascular, Renal and Metabolism, AstraZeneca Gothenburg, Sweden

*Corresponding author
Jan Oscarsson, Biopharmaceuticals R&D, Late-Stage Development, Cardiovascular, Renal and Metabolism, AstraZeneca, Gothenburg, Sweden; Tel: +46-31-7065785; Fax: +46-31-7763782; Email: Jan.oscarsson@astrazeneca.com

Submitted: 17 February 2020
Accepted: 25 February 2020
Published: 29 February 2020

Keywords
- Intra-abdominal fat
- Inflammation
- Liver
- Non-alcoholic fatty liver disease
- Pancreas

Abstract

Objective: Ectopic fat is associated with inflammation; whether ectopic fat in different tissues is differently associated with systemic inflammation is unclear. We compared the ectopic fat content of three tissues and investigated links with inflammation using inflammation-related proteins.

Materials and methods: Overall, 310 individuals from two trials (NCT02354976; NCT02279407) with body mass index ≥25 kg/m^2 and type 2 diabetes or serum triglycerides ≥1.7 mmol/L were included. Magnetic resonance imaging examinations included liver proton density fat fraction (PDFF), pancreatic fat percentage, and visceral adipose tissue (VAT) volume. Total body fat mass was evaluated by bioimpedance. Plasma levels of 74 inflammation-related proteins were measured with the proximity extension assay.

Results: Proteomic profiles differed between the tissues (P<0.0001) when adjusted for age, sex, fasting glucose, and total body fat mass. Using a split-sample discovery/validation approach, five proteins were significantly related to VAT and eight to liver PDFF; none were related to pancreatic fat. Fibroblast growth factor 21 and stem cell factor were related to VAT and liver PDFF. Oncostatin-M (P=0.001) was associated with VAT and the CUB domain-containing protein 1 with liver PDFF (P=0.00002).

Conclusion: Inflammation-related proteins were differently related to ectopic fat depots. Liver and visceral fat were linked to distinct inflammatory pathways; pancreatic fat was weakly linked to systemic inflammation.

ABBREVIATIONS

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; CI: Confidence Interval; CRP: C-Reactive Protein; FDR: False Discovery Rate; FGF21: Fibroblast Growth Factor 21; HDL-C: High-Density Lipoprotein Cholesterol; IL: Interleukin; LDL-C: Low-Density Lipoprotein Cholesterol; LFS: Liver Fat Score; MetS: Metabolic Syndrome; MRI: Magnetic Resonance Imaging; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; PDFF: Proton Density Fat Fraction; PEA: Proximity Extension Assay; SCF: Stem Cell Factor; SD: Standard Deviation; TNF-alpha: Tumor Necrosis Factor-alpha; VAT: Visceral Adipose Tissue

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by excess ectopic fat accumulation in the liver and affects 13%–30% of adults in population-based samples [1-3]. Inflammation is a distinct feature of NAFLD associated with progression to non-alcoholic steatohepatitis (NASH), and relationships have been demonstrated between liver fat content and circulating proinflammatory markers such as C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6 [4-7].

However, inflammatory markers are elevated not only in NAFLD but also in general obesity [8]. Intra-abdominal accumulation of ectopic fat (visceral adipose tissue [VAT]) is linked to both increased tissue expression [9,10] and systemic elevation of proinflammatory cytokines [11]. Moreover, VAT accumulation is associated with the development of NAFLD and liver fibrosis [12], and NAFLD is associated with increased adipose tissue inflammation [13].

In recent years, quantification of fat content has also been possible in the pancreas, which is another location of ectopic fat distribution. In contrast to liver fat, pancreatic fat is characterized by adipocyte infiltration [14]. Increased pancreatic

fat is a stronger determinant of reduced insulin secretion than VAT [15]. In addition, increased levels of pancreatic fat correlate with elevated levels of proinflammatory markers, although this association is markedly attenuated when adjusted for VAT [16].

Because the detection of NAFLD by histology or imaging techniques is expensive and cumbersome, several scores that use easily available clinical characteristics have been developed [17-19]. However, the C-statistics for those scores are not optimal, ranging between 0.80 and 0.83, and therefore require improvement.

The present study was conducted to compare the profiles of multiple inflammatory proteins in relation to three ectopic fat depots: VAT, liver, and pancreas. We hypothesized that the three depots are differently associated with inflammatory proteins. A secondary aim was to evaluate whether the addition of proteins found to be related to liver fat improves the predictive power of a validated score for NAFLD, the NAFLD liver fat score (LFS) [18].

MATERIALS AND METHODS

Patients and design

The study population comprised randomized patients as well as those who failed eligibility criteria during the screening phase of the two intervention trials, EFFECT I (NCT02354976) and EFFECT II (NCT02279407). These studies were approved by the Ethics Committee of Uppsala University. The EFFECT I and EFFECT II studies recruited patients from four and five different sites in Sweden, respectively. The results from these studies have been published earlier [20,21]. The studies were performed according to the Declaration of Helsinki and all patients had provided written informed consent. In brief, in the EFFECT I study, adult patients (aged 40-75 years) with a body mass index (BMI) of 25-40 kg/m^2, serum triglyceride levels ≥1.7 mM (150 mg/dL), and liver proton density fat fraction (PDFF) >5.5% were randomized. Patients with diabetes mellitus, a history of hepatic diseases, inability to undergo a magnetic resonance imaging (MRI) scan, and significant alcohol intake (over 14 units per week) were excluded [21].

Eligibility criteria for EFFECT II were similar to those for EFFECT I, with the exception that a history of type 2 diabetes was an inclusion criterion and presence of high serum triglyceride levels was not mandatory for inclusion [20].

Only baseline data from the screening phase in the EFFECT I and II studies were used in the present study. Data from 140 patients in EFFECT I and 170 patients in EFFECT II in whom a successful abdominal MRI scan was performed were used together in a unified sample (Table 1).

Patients were asked to fast overnight for a minimum of 10 hours for assessments the next morning. A weighing scale with bioimpedance was used for measuring body weight and total body fat mass (Tanita, Tokyo, Japan). Blood samples were collected, and plasma was frozen at −80˚C for later analysis of protein and other biomarkers.

Inflammation-related biomarkers

Plasma proteins were measured using the proximity extension assay (PEA) technique [22] on a commercial proteomics array with 92 preselected proteins known or suspected to be involved in inflammation (Olink, Uppsala, Sweden). Of the 92 proteins, 74 showed a call rate >75%, and these proteins were included for further analyses.

Other blood biomarkers

Plasma levels of glucose and insulin and serum levels of total cholesterol and triglycerides as well as serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured, as previously described [20,21]. Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) were determined at the local hospitals.

Quantification of ectopic fat depots using MRI

State-of-the-art MRI was used to quantify the fat depots, including the liver PDFF, by using the median of the fat fraction values inside the delineated total liver volume. Data were collected at seven imaging centers. Six of these used a 1.5T scanner and one used a 3T system. Dedicated water-fat separated scans were used for each measurement. The images were sent for centralized analysis at the Imaging Core Lab at Antaros Medical (Mölndal, Sweden). Measurements of VAT volumes and liver PDFF have been described previously [20,21]. Pancreatic fat was segmented from the axial slices of the water image by a trained operator using ImageJ software (Image J, NIH Software, Bethesda, MI). The border of the pancreas was avoided to reduce partial volume effects. PDFF was determined using the median of the fat fraction values inside the delineated pancreas volume. Repeated measurements from test-retest imaging of 10 healthy volunteers were performed to achieve an average standard deviation (SD) of 0.45 percentage points between the measurements.

NAFLD LFS

LFS was selected since it uses magnetic resonance spectroscopy rather than ultrasound for detection of NAFLD. The NAFLD LFS formula is as follows [18]:

−2.89 + (1.18×MetS) + (0.9×diabetes) + (0.15×insulin) + (0.04×AST) − 0.94×(AST/ALT),

Where MetS refers to metabolic syndrome classified per the International Diabetes Federation criteria [23].

Statistical methods

The protein levels were log transformed to achieve a normal distribution and thereafter transformed to an SD scale to facilitate comparison of the estimates in the regression models. Measurements of VAT, liver PDFF, and pancreatic fat percentage were also log transformed to achieve normal distributions.

The relationship between the three ectopic fat depots and total body fat mass was evaluated by pairwise correlation analysis using Pearson's correlation coefficient. Differences in protein profiles between the three ectopic fat depots were evaluated using multivariable linear regression. The 74 proteins were considered as dependent variables, and the three ectopic fat depots together with total body fat mass, age, and sex were considered as independent variables, with a single P-value to

assess whether the protein profile differed between the three ectopic fat depots.

Each of the 74 proteins was evaluated consecutively (as dependent variables) in relation to each of the three ectopic fat depots (as independent variables), with age, sex, and total body fat mass as confounders. This was conducted during a discovery step (a random two-thirds of the sample) and a validation step (one-third of the sample); only proteins with a false discovery rate (FDR) <0.05 in the discovery step were validated. The significance level was set at P<0.05 in the validation step.

Improvement in the discrimination of NAFLD was evaluated by comparison between two logistic regression models, with NAFLD as the binary outcome. The first model used only LFS as the independent variable, whereas the second model also included the proteins found to be related to liver fat (Table 2). C-statistics were used to calculate whether the addition of the proteins to LFS improved discrimination of NAFLD; P<0.05 was considered significant.

STATA 14 (Stata Inc, College Station, TX, USA) was used for statistical calculations. R 3.4.4 was used for the heat map in Figure 1.

RESULTS

The characteristics of the combined EFFECT population (n=310) are shown in Table 1. In brief, the mean age was 64.6 years, 61% were male, 45% had type 2 diabetes, mean BMI was 30.4 kg/m^2, mean liver PDFF was 13.2%, mean pancreatic fat percentage was 10.8%, and mean VAT volume was 3.5 L. The prevalence of NAFLD was 74% (defined as PDFF >5.5%).

Table 1: Baseline characteristics of the EFFECT sample (n=310).

Variable	Mean (SD) or proportion (%)
Age (years)	64.6 (7.2)
Sex, female	39
Systolic blood pressure (mm Hg)	143 (17)
Weight (kg)	90 (13)
Height (cm)	172 (9)
Waist circumference (cm)	107 (11)
BMI (kg/m^2)	30.4 (3.4)
Diabetes medication	41
Statin treatment	39
Antihypertensive treatment	57
Fasting glucose (mmol/L)	7.4 (2.0)
Fasting insulin (mU/L)	10.9 (6.9)
Serum cholesterol (mmol/L)	5.51 (1.41)
Serum triglycerides (mmol/L)	2.14 (1.16)
HDL-cholesterol (mmol/L)	1.34 (.37)
LDL-cholesterol (mmol/L)	3.47 (1.23)
Liver PDFF (%)	13.2 (9.5)
Pancreatic fat (%)	10.8 (7.7)
VAT volume (L)	3.5 (1.1)

BMI: Body Mass Index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; PDFF: Proton Density Fat Fraction; SD: Standard Deviation; VAT: Visceral Adipose Tissue

Table 2: Relationship between inflammation-related proteins and VAT volume and liver PDFF in the validation step.

Protein	Beta (95% CI)	*p-value*
VAT		
Fibroblast growth factor 21	31 (14, 49)	0.00055
Oncostatin-M	30 (12, 47)	0.00103
Stem cell factor	−33 (−52, −13)	0.0012
Matrix metalloproteinase-1	−24 (−14, −47)	0.017
Monocyte chemotactic protein 3	23 (13, 42)	0.018
Liver fat		
CUB domain-containing protein 1	42 (23, 60)	1.8E-05
Fibroblast growth factor 21	35 (17, 52)	0.00011
Hepatocyte growth factor	27 (11, 44)	0.0014
C-C motif chemokine 20	28 (6.9, 49)	0.011
Leukemia inhibitory factor receptor	22 (5.1, 40)	0.013
Interleukin-18	26 (5.7, 47)	0.014
Osteoprotegerin	22 (4.0, 41)	0.019
Stem cell factor	−22 (−42, −2.3)	0.031

Only proteins with p<0.05 in the validation step and FDR <0.05 in the discovery step are shown. Adjustments were made for age, sex, and total body fat mass. No protein was significantly related to pancreatic fat in the validation step.
CI: Confidence Interval; FDR: False Discovery Rate; PDFF: Proton Density Fat Fraction; VAT: Visceral Adipose Tissue

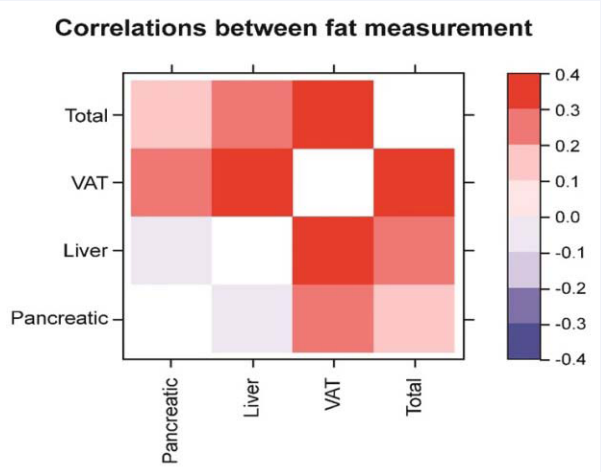

Figure 1 Pearson's correlation coefficient for pairwise relationships between fat measurements. All relationships with r>0.20 were significant (the two darkest red colors; P<0.01).
VAT: visceral adipose tissue

Total body fat mass was significantly correlated with liver PDFF and VAT volume, and VAT volume was significantly associated with both liver PDFF and pancreatic fat (P<0.01). However, there was no significant association between liver PDFF and pancreatic fat (Figure 1).

The total protein profile, comprising the 74 inflammation-related proteins, was related to the three ectopic fat depots in a significantly different manner (P<0.001; Figures S1-S3). The proteins were evaluated consecutively using the split-sample discovery/validation approach; five proteins were significantly related to VAT and eight to liver PDFF (Table 2).

None of the proteins were related to pancreatic fat percentage. Fibroblast growth factor 21 (FGF21) was positively related and stem cell factor (SCF) was negatively related to both VAT and liver PDFF. Oncostatin-M (P=0.001) was uniquely associated with VAT volume and the CUB domain-containing protein 1 was uniquely associated with liver PDFF (P=0.00002).

Further adjustment for diabetes generally reduced the magnitude of the relationships reported in Table 2; however, the relationships between matrix metalloproteinase-1 and VAT (P=0.3) and between leukemia inhibitory factor receptor and liver PDFF were no longer significant (P=0.1).

Addition of the eight proteins related to liver PDFF to the LFS non-significantly (P=0.1) increased C-statistics from 0.800 (95% confidence interval [CI] 0.743, 0.856) to 0.824 (95% CI 0.771, 0.876) in regard to NAFLD discrimination. Addition of single proteins to LFS also did not improve the discrimination significantly.

DISCUSSION

Consistent with earlier findings [24], the present study found a relationship between VAT volume and liver PDFF. However, pancreatic fat percentage was not related to liver PDFF in the study population. Furthermore, a panel of 74 inflammation-related proteins was differently related to the three ectopic fat depots. Separate investigation of each protein showed that FGF21 and SCF were related to both liver PDFF and VAT volume, whereas several other proteins were significantly related to either liver PDFF or VAT volume. No protein was found to be significantly related to pancreatic fat percentage.

Previous studies have shown that some proinflammatory cytokines, such as IL-6, TNF alpha, and CRP are associated with ectopic fat accumulation in the liver, pancreas, and VAT [4-7,11,13]. Our study adds to these observations by including several other inflammation-related markers. The aim of our study was to determine whether different ectopic fat depots are differently associated with inflammatory-related proteins. As such, the analysis was adjusted for total body fat mass owing to the link between general obesity and CRP and proinflammatory cytokines [25]. Removing the influence of general obesity from the analysis would thus make differences between the fat depots more evident.

Increased FGF21 levels have been linked to excess body fat [26], and in particular, liver fat accumulation [27]. In patients undergoing gastric bypass surgery, the degree of reduction in liver fat was correlated with the magnitude of decline in FGF21 levels [26], exemplifying the link between liver fat and FGF21. In our study, plasma FGF21 levels were associated with both liver PDFF and VAT following adjustment for total body fat mass, underpinning the link between ectopic fat accumulation and FGF21. During energy excess and increased ectopic fat stores, plasma FGF21 levels are increased, apparently in parallel with increased insulin resistance [28]. However, the role of elevated FGF21 levels in ectopic fat accumulation is unclear, but may reflect an "FGF21-resistance" in individuals with increased ectopic fat and should be regarded as a compensatory mechanism [29]. A compensatory increase in FGF21 levels may be explained by the association between mitochondrial dysfunction and endoplasmic reticulum stress and high FGF21 production. FGF21 is a biomarker for muscle-manifested mitochondrial chain deficiencies in children [30]. Moreover, experimentally induced mitochondrial dysfunction, either by knocking out *CPT1b* (long-chain fatty acid oxidation) or *Atg7* (autophagy) or by increasing mitochondrial uncoupling, increases FGF21 expression in the liver and skeletal muscle [31-33].

Receptor tyrosine kinase KIT and its ligand, SCF, are involved in the growth and maintenance of many cell types. The serum levels and expression of SCF in adipose tissue are increased in both obese mice and humans with obesity, and systemic overexpression of SCF in mice reduces fat mass [34]. Thus, high SCF levels are coupled with increased thermogenesis. As such, the negative association between SCF and liver PDFF and VAT volume in our study indicates that low levels of SCF are associated with increased ectopic fat accumulation in humans.

Apart from these two proteins being significantly associated with both VAT and liver fat, three proteins were significantly related to VAT alone and another group of six proteins were significantly related to liver fat. Whether some of these proteins are linked to the development of NAFLD remains to be studied. However, the association of different inflammatory proteins with liver fat and VAT adds to previous findings showing that these ectopic fat stores, independent of each other, seem to contribute to the variation in plasma levels of triglycerides, HDL-C, insulin as well as insulin sensitivity [24].

In the present study, no significant associations were found between the investigated inflammatory markers and pancreatic fat percentage. As observed in the caterpillar plot in Figure S3, several proteins were related to pancreatic fat percentage with a P-value <0.05 in the total sample. Nevertheless, the lack of a significant correlation in this study does not exclude the possibility of a relationship between the two factors since the discovery/validation approach used should lead to a low risk of false-positive. Limited data exist on the link between pancreatic fat and inflammation, although some studies have suggested that pancreatic fat is associated with insulin resistance but not with progression of type 2 diabetes [35,36]. It remains to be elucidated whether an association between pancreatic fat and inflammation indeed exists. Another potential reason for the absence of a validated relationship between pancreatic fat and inflammation-related proteins is the small volume and more diffuse borders of the pancreas, which make it difficult to define the volume, leading to large variations in measurements that in turn preclude conclusive results.

Using the Reactome database (https://reactome.org/PathwayBrowser/), the different pathways associated with the identified proteins of interest (Table S1) were investigated. As expected by the selection of the proteins on the chip used, most were linked to different pathways related to immune activation.

However, several other pathways, such as lipoprotein metabolism, cellular hexose transport, PI3K/AKT signaling, RAF/MAP kinase cascade, receptor tyrosine kinase signaling, collagen metabolism, and proliferation of vascular smooth muscle cells, were also associated with the identified proteins (Table S1). Some of these pathways may be involved in the development of NAFLD or an expansion of VAT; however, they could also be a consequence of NAFLD and/or ectopic fat accumulation in the abdominal cavity.

Although eight proteins showed a high degree of association with liver fat, the addition of these proteins to an established score to predict NAFLD [18] increased the predictive power (discrimination) to a limited, non-significant degree. Thus, the information provided by the variables already included in the LFS was presumably similar to that provided by inclusion of the eight proteins, despite adjustment for total body fat mass. It may be speculated that the inflammatory proteins associated with liver PDFF may be useful to discriminate non-alcoholic fatty liver from NASH.

Strength of this study is that several inflammation-related plasma proteins were measured and three different ectopic fat depots were quantified by MRI. However, the study also has limitations. An independent population was not available for replication of the results and, therefore, the split-sample technique was used within the same sample for validation. In addition, only individuals who were overweight/obese with a high risk of NAFLD and increased VAT volume and pancreatic fat were included in this study; therefore, the results must be reproduced in a population-based sample for generalizability.

CONCLUSION

In summary, different inflammation-related proteins in plasma were differently associated with liver and visceral fat depots, indicating that these depots are linked to inflammation in different ways. In contrast, the link between inflammation and pancreatic fat is less evident and needs further investigation in interventional studies. Moreover, the addition of proteins related to liver fat did not improve the predictive power of LFS.

CLINICAL TRIAL REGISTRATION

EFFECT I: NCT02354976;

https://clinicaltrials.gov/ct2/show/NCT02354976

EFFECT II: NCT02279407;

https://clinicaltrials.gov/ct2/show/NCT02279407

ACKNOWLEDGMENT

The authors thank the study participants, investigators, and study staff at the recruiting hospitals. Editorial assistance was provided by Cactus Life Sciences (part of Cactus Communications) and funded by AstraZeneca.

Funding Acknowledgment

The study was funded by AstraZeneca.

Author Contributions

All authors were involved in writing the paper and had final approval of the submitted and published versions.

Data Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at

https://astrazenecagrouptrials.pharmacm.com

/ST/Submission/Disclosure.

REFERENCES

1. Bellentani S, Saccoccio G, Masutti F. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med. 2000; 132: 112-117.
2. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40: 1387-1395.
3. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018; 67: 328-357.
4. Kim YC, Cho YK, Lee WY, Kim HJ, Park JH, Park DI, et al. Serum adipocyte-specific fatty acid-binding protein is associated with nonalcoholic fatty liver disease in apparently healthy subjects. J Nutr Biochem. 2011; 22: 289-292.
5. Genc H, Dogru T, Kara M, Tapan S, Ercin CN, Acikel C, et al. Association of plasma visfatin with hepatic and systemic inflammation in nonalcoholic fatty liver disease. Ann Hepatol. 2013; 12: 548-555.
6. Kogiso T, Moriyoshi Y, Shimizu S, Nagahara H, Shiratori K. High-sensitivity C-reactive protein as a serum predictor of nonalcoholic fatty liver disease based on the Akaike Information Criterion scoring system in the general Japanese population. J Gastroenterol. 2009; 44: 313-321.
7. Francque SM, van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: pathophysiological mechanisms and implications. J Hepatol. 2016; 65: 425-443.
8. Wensveen FM, Valentić S, Šestan M, Turk Wensveen T, Polić B. The "Big Bang" in obese fat: events initiating obesity-induced adipose tissue inflammation. Eur J Immunol. 2015; 45: 2446-2456.
9. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004; 145: 2273-2782.
10. Bruun JM, Lihn AS, Madan AK, Pedersen SB, Schiøtt KM, Fain JN, et al. Higher production of IL-8 in visceral vs. subcutaneous adipose tissue. Implication of nonadipose cells in adipose tissue. Am J Physiol Endocrinol Metab. 2004; 286: E8-E13.
11. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation. 2007; 116: 1234-1241.
12. Eguchi Y, Mizuta T, Sumida Y, Ishibashi E, Kitajima Y, Isoda H, et al. The pathological role of visceral fat accumulation in steatosis, inflammation, and progression of nonalcoholic fatty liver disease. J Gastroenterol. 2011; 46 Suppl 1: 70-78.
13. du Plessis J, van Pelt J, Korf H, Mathieu C, van der Schueren B, Lannoo M, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. Gastroenterology. 2015; 149: 635-648.e14.

14. Pinnick KE, Collins SC, Londos C, Gauguier D, Clark A, Fielding BA. Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. Obesity (Silver Spring). 2008; 16: 522-530.

15. Heni M, Machann J, Staiger H, Schwenzer NF, Peter A, Schick F, et al. Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: a nuclear magnetic resonance study. Diabetes Metab Res Rev. 2010; 26: 200-205.

16. Lê KA, Ventura EE, Fisher JQ, Davis JN, Weigensberg MJ, Punyanitya M, et al. Ethnic differences in pancreatic fat accumulation and its relationship with other fat depots and inflammatory markers. Diabetes Care. 2011; 34: 485-490.

17. Cheung CL, Lam KS, Wong IC, Cheung BM. Non-invasive score identifies ultrasonography-diagnosed non-alcoholic fatty liver disease and predicts mortality in the USA. BMC Med. 2014; 12: 154.

18. Kotronen A, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology. 2009; 137: 865-872.

19. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010; 42: 503-508.

20. Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnström M, Moris L, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia. 2018; 61: 1923-1934.

21. Oscarsson J, Önnerhag K, Risérus U, Sundén M, Johansson L, Jansson PA, et al. Effects of free omega-3 carboxylic acids and fenofibrate on liver fat content in patients with hypertriglyceridemia and non-alcoholic fatty liver disease: a double-blind, randomized, placebo-controlled study. J Clin Lipidol. 2018; 12: 1390-1403.e4.

22. Assarsson E, Lundberg M, Holmquist G, Björkesten J, Thorsen SB, Ekman D, Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. PLoS One. 2014; 9: e95192.

23. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005; 366: 1059-1062.

24. Kotronen A, Yki-Järvinen H, Sevastianova K, Bergholm R, Hakkarainen A, Pietiläinen KH, et al. Comparison of the relative contributions of intra-abdominal and liver fat to components of the metabolic syndrome. Obesity (Silver Spring). 2011; 19: 23-28.

25. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444: 860-867.

26. Fjeldborg K, Pedersen SB, Møller HJ, Richelsen B. Reduction in serum fibroblast growth factor-21 after gastric bypass is related to changes in hepatic fat content. Surg Obes Relat Dis. 2017; 13: 1515-1523.

27. Tyynismaa H1, Raivio T, Hakkarainen A, Ortega-Alonso A, Lundbom N, Kaprio J, et al. Liver fat but not other adiposity measures influence circulating FGF21 levels in healthy young adult twins. J Clin Endocrinol Metab. 2011; 96: E351-E355.

28. Iggman D, Rosqvist F, Larsson A, Arnlöv J, Beckman L, Rudling M, et al. Role of dietary fats in modulating cardiometabolic risk during moderate weight gain: a randomized double-blind overfeeding trial (LIPOGAIN study). J Am Heart Assoc. 2014; 3: e001095.

29. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, et al. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes. 2010; 59: 2781-2789.

30. Suomalainen A, Elo JM, Pietiläinen KH, Hakonen AH, Sevastianova K, Korpela M, et al. FGF-21 as a biomarker for muscle manifesting mitochondrial respiratory chain deficiencies: a diagnostic study. Lancet Neurol. 2011; 10: 806-818.

31. Kim KH, Jeong YT, Oh H, Kim SH, Cho JM, Kim YN, et al. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. Nat Med. 2013; 19: 83-92.

32. Vandanmagsar B, Warfel JD, Wicks SE, Ghosh S, Salbaum JM, Burk D, et al. Impaired mitochondrial fat oxidation induces FGF21 in muscle. Cell Rep. 2016; 15: 1686-1699.

33. Keipert S, Ost M, Johann K, Imber F, Jastroch M, van Schothorst EM,et al. Skeletal muscle mitochondrial uncoupling drives endocrine cross-talk through the induction of FGF21 as a myokine. Am J Physiol Endocrinol Metab. 2014; 306: E469-E482.

34. Huang Z, Ruan HB, Xian L, Chen W, Jiang S, Song A, et al. The stem cell factor/Kit signalling pathway regulates mitochondrial function and energy expenditure. Nat Commun. 2014; 5: 4282.

35. Tushuizen ME, Bunck MC, Pouwels PJ, Bontemps S, van Waesberghe JH, Schindhelm RK, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. Diabetes Care. 2007; 30: 2916-2921.

36. Catanzaro R, Cuffari B, Italia A, Marotta F. Exploring the metabolic syndrome: nonalcoholic fatty pancreas disease. World J Gastroenterol. 2016; 22: 7660-7675.

Cite this article

Lind L, Risérus U, Kullberg J, Ahlström H, Eriksson JW, et al. (2020) Inflammation-Related Proteins Are Differently Associated With Visceral Adipose Tissue, Liver Fat, and Pancreatic Fat. JSM Gastroenterol Hepatol 7(1): 1094.