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Intermuscular adipose tissue is associated with monocyte chemoattractant protein-1, independent of visceral adipose tissue

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Abstract

Objectives—Emerging evidence suggests that intermuscular adipose tissue is a risk factor for insulin resistance, but the underlying mechanism still remains unclear. We investigated whether the levels of leptin, adiponectin and monocyte chemoattractant protein-1 are associated with intermuscular adipose tissue in obese subjects.

Design and Methods—A cross-sectional study was performed on 77 obese Korean women. Areas of visceral adipose tissue, subcutaneous adipose tissue and intermuscular adipose tissue were measured by computed tomography scan, and serum concentrations of adipokines were measured by enzyme-linked immunosorbent assays. Correlation between the levels of adipokines and the fat areas was assessed using Pearson correlation and covariate-adjusted multivariable regression.

Results—Leptin was positively correlated with subcutaneous adipose tissue ($r = 0.452$, $P < 0.001$), fasting insulin ($r = 0.403$, $P < 0.001$) and homeostasis model assessment of insulin resistance ($r = 0.360$, $P = 0.001$), whereas monocyte chemoattractant protein-1 was positively correlated with intermuscular adipose tissue ($r = 0.483$, $P < 0.001$). After adjustment for age, height, and other body composition metrics, leptin was still related to subcutaneous adipose tissue

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Conflicts of interest statement

The authors declare no conflicts of interest.

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($\beta = 0.390$, $P = 0.001$). Monocyte chemoattractant protein-1 was associated with intermuscular adipose tissue ($\beta = 0.433$, $P = 0.001$) after adjustment for visceral adipose tissue.

Conclusions—Intermuscular adipose tissue was correlated with monocyte chemoattractant protein-1, suggesting its role in the development of insulin resistance.

Keywords

Obesity; MCP-1; adiponectin; leptin; intermuscular adipose tissue

1. Introduction

Ectopic fat is lipid accumulated in tissues that typically do not store large amount of fat, such as liver, vessel and skeletal muscle and is a major risk factor for metabolic syndrome. Visceral adipose tissue (VAT¹) and intermuscular adipose tissue (IMAT²) are the main contributors of ectopic fat [1] and have been shown to increase the risk of developing insulin resistance and cardiovascular diseases [2–4]. Adipokines such as monocyte chemoattractant protein 1 (MCP-1³), leptin and adiponectin are secreted from adipose tissue and play a critical role in obesity-related insulin resistance, altered lipid metabolism and inflammatory response [5].

MCP-1 mediates the attraction of monocytes and T lymphocytes to sites of inflammation [6] and maintains a proinflammatory state during the development of metabolic syndrome [7]. Previous studies have shown that the levels of MCP-1 are elevated in metabolic syndrome [8, 9]. In addition, it has been shown that MCP-1, via activation of extracellular signal-regulated kinase (ERK) 1/2 pathways, causes an increase in the expression of amylin in pancreatic beta cells and insulin resistance [10, 11].

Leptin has been known as a critical regulator of energy balance, which acts centrally to suppress feeding behavior while stimulating energy expenditure [12]. Clinical studies have shown that leptin levels are associated with insulin resistance and metabolic syndrome [13–15]. In contrast, adiponectin has insulin-sensitizing, anti-inflammatory and anti-atherogenic effects [6, 16] through adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR) pathways [17].

In recent years much attention has been paid to the relationship between VAT and adipokines. It has been well shown that VAT is positively associated with MCP-1 but negatively correlated with adiponectin [18–20], which might mediate the VAT-induced cardiovascular diseases and insulin resistance. The role of IMAT in the pathophysiology of obesity-related diseases, however, is not very clear. Even though the role of IMAT has been also implicated in metabolic syndrome [21–23], the relationships between IMAT and adipokines are not well understood. Therefore, we investigated whether the levels of MCP-1, leptin and adiponectin are related to IMAT in obese Korean women.

¹VAT, visceral adipose tissue

²IMAT, intermuscular adipose tissue

³MCP-1, monocyte chemoattractant protein 1

2. Material and methods

2.1. Study subjects

The subjects in our cross-sectional study were enrolled from adults who visited the obesity clinic of CHA Bundang Medical Center. We recruited 77 obese women with a body mass index (BMI⁴) ≥ 25 kg/m² from December 2011 to March 2012. It is noteworthy that obesity-related morbidity and mortality occur at lower BMIs in Asian populations, and the cutoffs for overweight and obesity in Asian populations should be lower than the general WHO criteria (23.0 kg/m² and 25.0 kg/m², respectively) according to the recent guidelines for Asia-Pacific populations [24, 25]. All subjects voluntarily took part in our study without any reward and submitted informed consents. We did not include any subjects with hypertension, diabetes, renal disease, malignant disease, thyroid disease, collagen diseases or infections. Patients with smoking history were excluded. This study was approved by the IRB of CHA Bundang Medical Center.

2.2. Medical history and life-style habits

The medical history, medication and lifestyle habits of the subjects were collected. The subjects who drink alcohol once a month or more frequently were regarded as alcohol consumers. Physical activity was assessed using records provided by the individual subjects. All subjects were trained to document their daily activities (e.g. driving a car, cooking, bathing, showering and resting) and diet for three days before the visit. Energy expenditure was calculated according to the metabolic expenditure table (Perspectives in Nutrition, 2nd edition). Calorie intake was determined using records provided by the individual subjects. All the records were analyzed using the Computer Aided Nutritional analysis program (CAN) - Pro 3.0 (The Korean Nutrition Society, Korea).

2.3. Anthropometric measurements

Height and weight were measured in centimeters and kilograms, respectively, to the first decimal place with the subjects standing shoeless on a firm surface. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured midway between the lower rib margin and the iliac crest in a standing position. Sitting blood pressure was measured following a 10-minute rest using a sphygmomanometer with an appropriate cuff size.

2.4. Biochemical measurements

Blood samples, after an 8 hour fast, were collected and brought to the central testing institute (Seoul medical science Institute, Korea). Fasting glucose levels were examined using the automated glucose oxidase method using the Hitachi DP modular (D2400 P800, Hitachi, Tokyo, Japan). Insulin levels were measured using electrochemiluminescence immunoassay (ECLIA) with the Cobas 8000 modular analyzer (Hitachi, Tokyo, Japan). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR⁵) was determined by fasting glucose (mg/dL) multiplied by fasting insulin (uIU/mL) divided by 405. Serum samples for

⁴BMI, body mass index

⁵HOMA-IR, homeostatic model assessment of insulin resistance

adipokine assay were stored at -70°C and analyzed at once after collecting all samples. Leptin and MCP-1 levels were determined by enzyme linked immunosorbent assay (ELISA; human leptin ELISA kit, Millipore Inc., Germany and eBioscience Inc., San Diego, USA). The levels of adiponectin were measured using the ELISA (DuoSet ELISA Development kit; R&D Systems, Minneapolis, MN, USA).

2.5. Measurements of body composition

Total fat and lean mass were measured using dual-energy x-ray absorptiometry (DXA) (Hologic Discovery W, Hologic Inc., Bedford, MA) to calculate the body fat percentage. Images from the region between L4 and L5, and the mid-thigh level were obtained using the multi-slice computed tomography scan (Somatom Sensation 16, Siemens, Erlangen, Germany). The fat areas were estimated in the range of -150 to -50 Hounsfield units (HU). The abdominal muscular wall was delineated using a manually drawn line to separate the VAT from the subcutaneous adipose tissue (SAT⁶). IMAT was the fat area inside the muscle line manually drawn at the mid-thigh image. The areas that had attenuation values between 0 and 34 HU were considered as low-density muscle which indicates fat-rich muscle; the areas that had attenuation values between 35 and 100 were regarded as high-density muscle which indicates normal muscle. The thigh muscle cross-sectional area was a sum of the two muscle areas.

2.6. Statistical analysis

The SPSS 21.0 statistical analysis software (IBM, Armonk, NY, USA) was used to perform all data analyses. To assess the relationship among the adipokine levels, body compositions, and metabolic parameters, Pearson's correlation analysis was used. Subjects were divided to two groups according to the median value of MCP-1, leptin and adiponectin levels. The subgroup comparisons between the high adipokine group and low adipokine group were evaluated using the unpaired Student's *t*-test. We used covariate-adjusted multivariable regression to examine the relationship between adipokine levels and body composition metrics with adjustment for age, height and other body composition confounders. For all analyses, a *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of the study participants

Subject characteristics are presented in Table 1. The mean age of the 77 subjects was 41.7 ± 10.9 years old, and their mean BMI was 28.4 ± 2.2 kg/m². The mean blood MCP-1, leptin, and adiponectin levels were 98.8 ± 54.2 pg/mL, 17.9 ± 8.2 ng/mL, and 2.8 ± 1.3 µg/mL, respectively. The mean body fat percentage measured by DXA was $39.0 \pm 4.0\%$. The mean VAT and SAT measured by CT were 104.7 ± 31.6 and 283.1 ± 77.6 cm², respectively. The mean high-density muscle was 91.8 ± 15.6 cm². The average SAT levels of our subjects (283.1 cm²) were 50–60 % higher than those of general population ($173.1 - 183.5$ cm²). In addition, the average VAT levels of our subjects (104.7 cm²) were 20–30 % higher than

⁶SAT, subcutaneous adipose tissue

those of general population (80.0 – 90.1 cm²) and were comparable to the cutoff to diagnose central obesity [26, 27].

3.2. Pearson correlation analysis of adipokines with metabolic variables, body composition

Using Pearson correlation analysis, the associations between adipokines and fat distribution were examined (Table 2). MCP-1 level was positively correlated with the low-density muscle ($r = 0.355$, $P = 0.002$) and IMAT ($r = 0.483$, $P < 0.001$). The positive trend in the relationship was demonstrated between the levels of MCP-1 and VAT ($r = 0.204$, $P = 0.076$). Leptin level was positively correlated with BMI ($r = 0.411$, $P < 0.001$), body fat percentage ($r = 0.480$, $P < 0.001$), total abdominal fat area ($r = 0.479$, $P < 0.001$), and SAT ($r = 0.452$, $P < 0.001$). The relationship was not significant between adiponectin and any of the body composition metrics.

For metabolic parameters, leptin was positively correlated with fasting insulin level ($r = 0.403$, $P < 0.001$) and HOMA-IR ($r = 0.360$, $P = 0.001$). In contrast, there was no significant association between the levels of MCP-1 and metabolic parameters. A negative trend was observed between the levels of adiponectin and HOMA-IR ($r = -0.202$, $P = 0.078$).

3.3. Subgroup comparisons between the high adipokine groups and low adipokines group

Using the Student's unpaired *t*-test, we compared the high adipokine groups and low adipokines group (Figure 1). Fasting plasma glucose levels in the subjects with high MCP-1, leptin and adiponectin levels were not significantly different from those in subjects with low adipokines levels. Subjects with high leptin levels showed significantly higher levels of insulin and HOMA-IR compared to the subjects with low leptin levels. Subjects with high adiponectin levels, however, showed significant lower levels of insulin and HOMA-IR than the subjects with low adiponectin levels. Subject with high MCP-1 showed higher insulin levels and increased insulin resistance than other groups, but the difference did not reach statistical significance.

3.4. Multivariate linear regression analyses of adiposity measures with MCP-1, Leptin and Adiponectin

Multivariate linear regression analyses were performed to examine the relationships between adipokines and specific body compositions with adjustments for confounders such as age, height and other body composition metrics (Table 3). MCP-1 ($\beta = 0.476$, $P < 0.001$) and leptin ($\beta = 0.223$, $P = 0.049$) were associated with IMAT after adjustments for age and height. The association between MCP-1 and IMAT was still significant even after further adjustments for VAT, SAT and high-density muscle ($\beta = 0.433$, $P = 0.001$). However, association between leptin levels and IMAT was not significant after adjustments for VAT, SAT and high-density muscle ($\beta = -0.051$, $P = 0.686$). Leptin was independently associated with SAT ($\beta = 0.390$, $P = 0.001$), high-density muscle ($\beta = -0.317$, $P = 0.031$) and VAT ($\beta = 0.248$, $P = 0.041$) after adjustments for age, height, and other body composition metrics. There was no significant correlation between the levels of adiponectin and body composition.

4. Discussion

Our study examined the associations between the adipokines and IMAT in obese women. MCP-1 was associated with IMAT, independently of VAT and SAT. Higher serum levels of leptin were related to higher SAT and VAT, and lower high-density muscle area.

Previous studies have well shown that adipose macrophages play a significant role in the immune response system and insulin resistance. MCP-1 is one of the major adipokines secreted from adipose macrophages, causing the aggregation of monocytes and T lymphocytes and maintaining a proinflammatory status in metabolic dysfunction [28, 29]. It has been shown that MCP-1 upregulates the expression of amylin in pancreatic beta cell through ERK pathway and contributes to the increase in insulin resistance [10, 11, 30]. In this study, the subjects with high MCP-1 levels showed increased levels of HOMA-IR and insulin compared to the subjects with low MCP-1 levels, but the difference did not reach statistical significance, which might be due to the relatively small sample size. Previous studies also have shown that VAT, compared to SAT, contains more macrophages and secretes higher levels of MCP-1 [19, 20, 31, 32]. Consistent with the previous studies, our results showed a positive trend of correlation between MCP-1 and VAT, but not with SAT. However, the association between MCP-1 and VAT did not reach statistical significance after adjustment for other confounding factors such as age, height, and other body composition metrics. Interestingly, our study also revealed that MCP-1 is significantly correlated with IMAT independent of VAT. It has been suggested that IMAT is a subtype of perivascular fat tissue as it is found around muscle resistant arteries [33]. Previous studies have shown that perivascular fat tissue plays a major role in MCP-1 release, which may explain the correlation between IMAT and MCP-1 that we have observed in the study [34]. IMAT has been regarded as an important marker for the metabolic risks such as insulin resistance and inflammation [35, 36], but the underlying mechanism has yet been well understood. We demonstrate that IMAT area is positively correlated with MCP-1 levels, implicating the role of IMAT in the regulation of MCP-1 release.

Leptin is a key modulator in energy metabolism [37] which has been implicated in the etiology of insulin resistance [38, 39]. In accordance with previous findings, our study revealed that leptin is positively correlated with HOMA-IR and insulin. Previous studies have shown that the levels of leptin are closely correlated with the area of SAT [40, 41]. In addition, Van Harmelen V et al. showed that SAT secretes more leptin because SAT is the major depot of adipose tissue and has higher releasing activity per fat cell than VAT [42]. Consistent with the previous reports, we showed that high SAT area was related to high leptin level. A previous experimental study showed that exogenous leptin reduces protein synthesis of myocytes, demonstrating the negative relationship between leptin and high-density muscle area [43]. Katsuhiko Kohara et. al showed that serum level of leptin is negatively correlated with thigh muscle cross sectional area, which is composed of high and low-density muscle area [44]. We found that high-density muscle area was inversely associated with leptin level. Moreover, after adjustment for VAT, leptin was still significantly correlated with both SAT and thigh high-density muscle area. In our study, there was a weak positive correlation between leptin levels and VAT.

Adiponectin has been known to play an important role in protecting against insulin resistance and atherosclerosis by affecting adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator activated receptor (PPAR) pathways [17]. Similar to previous reports, we show that subjects with higher adiponectin levels have lower levels of HOMA-IR and insulin compared to other groups. In a previous study, adiponectin was negatively related to VAT [18]. However, we did not find any significant correlation of adiponectin levels with IMAT and VAT. The discrepancy may arise from the fact that subjects of our study were obese patients (BMI: 26.2 ~30.8 kg/m²; 95 % confidence interval) whereas the previous study used both lean and obese individuals (BMI: 22.1~30.7 kg/m²; 95 % confidence interval) [18].

There are limitations in our study. First, the sample size was relatively small. However, the subjects of our study were rather homogeneous: Korean women whose BMI falls between 25 and 30. The homogeneity can significantly minimize the variability that arises from different populations of subjects. Second, we employed the cross-sectional design rather than the longitudinal approach. Long-term follow-up is needed to clarify the systemic effects of the adipokines and body fat distribution.

In conclusion, our study demonstrates that IMAT, but not VAT, is correlated with MCP-1 whereas SAT is correlated with leptin. IMAT, as a type of ectopic fat, has been implicated as a risk factor for diabetes and cardiovascular diseases, but the pathophysiology of the diseases has not been well understood. Our finding that shows the correlation between IMAT and MCP-1 suggests that MCP-1 from IMAT may play a role in the development of diseases. Further studies are required to address the cause and effect relationship of the correlation.

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References

1. Britton KA, Fox CS. Ectopic fat depots and cardiovascular disease. *Circulation*. 2011; 124:e837–41. [PubMed: 22156000]
2. Ding J, Hsu FC, Harris TB, Liu Y, Kritchevsky SB, Szklo M, et al. The association of pericardial fat with incident coronary heart disease: The multi-ethnic study of atherosclerosis (mesa). *The American journal of clinical nutrition*. 2009; 90:499–504. [PubMed: 19571212]
3. Krssak M, Falk Petersen K, Dresner A, DiPietro L, Vogel SM, Rothman DL, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: A 1h nmr spectroscopy study. *Diabetologia*. 1999; 42:113–6. [PubMed: 10027589]
4. Lehman SJ, Massaro JM, Schlett CL, O'Donnell CJ, Hoffmann U, Fox CS. Peri-aortic fat, cardiovascular disease risk factors, and aortic calcification: The framingham heart study. *Atherosclerosis*. 2010; 210:656–61. [PubMed: 20152980]
5. Scherer PE. Adipose tissue: From lipid storage compartment to endocrine organ. *Diabetes*. 2006; 55:1537–45. [PubMed: 16731815]
6. Inadera H. The usefulness of circulating adipokine levels for the assessment of obesity-related health problems. *International journal of medical sciences*. 2008; 5:248–62. [PubMed: 18773088]

7. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006; 444:875–80. [PubMed: 17167476]
8. Kim CS, Park HS, Kawada T, Kim JH, Lim D, Hubbard NE, et al. Circulating levels of mcp-1 and il-8 are elevated in human obese subjects and associated with obesity-related parameters. *International journal of obesity*. 2006; 30:1347–55. [PubMed: 16534530]
9. Piemonti L, Calori G, Mercalli A, Lattuada G, Monti P, Garancini MP, et al. Fasting plasma leptin, tumor necrosis factor- α receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women: Impact on cardiovascular mortality. *Diabetes care*. 2003; 26:2883–9. [PubMed: 14514596]
10. Cai K, Qi D, Hou X, Wang O, Chen J, Deng B, et al. Mcp-1 upregulates amylin expression in murine pancreatic beta cells through erk/jnk-ap1 and nf-kappab related signaling pathways independent of ccr2. *PloS one*. 2011; 6:e19559. [PubMed: 21589925]
11. Ashida N, Arai H, Yamasaki M, Kita T. Distinct signaling pathways for mcp-1-dependent integrin activation and chemotaxis. *The Journal of biological chemistry*. 2001; 276:16555–60. [PubMed: 11278464]
12. Piya MK, McTernan PG, Kumar S. Adipokine inflammation and insulin resistance: The role of glucose, lipids and endotoxin. *The Journal of endocrinology*. 2013; 216:T1–T15. [PubMed: 23160966]
13. Soodini GR. Adiponectin and leptin in relation to insulin sensitivity. *Metabolic syndrome and related disorders*. 2004; 2:114–23. [PubMed: 18370642]
14. Zuo H, Shi Z, Yuan B, Dai Y, Wu G, Hussain A. Association between serum leptin concentrations and insulin resistance: A population-based study from china. *PloS one*. 2013; 8:e54615. [PubMed: 23349940]
15. Lee, Eun Sang, MD; Lee, Don Haeng, MD; Kim, Seung Youn, MD; Kim, Jin Young, MD; Kim, Wha Sook, MD; Lee, Hoon Jae, MD; Choi, Won, MD; Kim, Pum Soo, MD; Kim, Hyung Gil, MD; Kim, Young Soo, MD . Relationship between blood leptin and non alcoholic fatty liver in obese male adolescent. *Korean Journal of Medicine*. 2001; 61
16. Guzik TJ, Mangalat D, Korb R. Adipocytokines - novel link between inflammation and vascular function? *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society*. 2006; 57:505–28. [PubMed: 17229978]
17. Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T. Adiponectin receptors: A review of their structure, function and how they work. *Best practice & research Clinical endocrinology & metabolism*. 2014; 28:15–23. [PubMed: 24417942]
18. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: Evidence for independent roles of age and sex. *Diabetologia*. 2003; 46:459–69. [PubMed: 12687327]
19. Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (at): Implication of macrophages resident in the at. *The Journal of clinical endocrinology and metabolism*. 2005; 90:2282–9. [PubMed: 15671098]
20. Malavazos AE, Cereda E, Morricone L, Coman C, Corsi MM, Ambrosi B. Monocyte chemoattractant protein 1: A possible link between visceral adipose tissue-associated inflammation and subclinical echocardiographic abnormalities in uncomplicated obesity. *European journal of endocrinology/European Federation of Endocrine Societies*. 2005; 153:871–7. [PubMed: 16322393]
21. Yim JE, Heshka S, Albu J, Heymsfield S, Kuznia P, Harris T, et al. Intermuscular adipose tissue rivals visceral adipose tissue in independent associations with cardiovascular risk. *International journal of obesity*. 2007; 31:1400–5. [PubMed: 17452994]
22. Durheim MT, Slentz CA, Bateman LA, Mabe SK, Kraus WE. Relationships between exercise-induced reductions in thigh intermuscular adipose tissue, changes in lipoprotein particle size, and visceral adiposity. *American journal of physiology Endocrinology and metabolism*. 2008; 295:E407–12. [PubMed: 18544640]

23. Therkelsen KE, Pedley A, Speliotes EK, Massaro JM, Murabito J, Hoffmann U, et al. Intramuscular fat and associations with metabolic risk factors in the framingham heart study. *Arteriosclerosis, thrombosis, and vascular biology*. 2013; 33:863–70.
24. Committee S. The asia-pacific perspective: Redefining obesity and its treatment. Melbourne: International Diabetes Institute; 2000. p. 11–2.
25. Kim MK, Lee WY, Kang JH, Kang JH, Kim BT, Kim SM, et al. 2014 clinical practice guidelines for overweight and obesity in korea. *Endocrinology and metabolism*. 2014; 29:405–9. [PubMed: 25559568]
26. Kim S, Cho B, Lee H, Choi K, Hwang SS, Kim D, et al. Distribution of abdominal visceral and subcutaneous adipose tissue and metabolic syndrome in a Korean population. *Diabetes care*. 2011; 34:504–6. [PubMed: 21228245]
27. Park YS, Kwon HT, Hwang SS, Choi SH, Cho YM, Lee J, et al. Impact of visceral adiposity measured by abdominal computed tomography on pulmonary function. *Journal of Korean medical science*. 2011; 26:771–7. [PubMed: 21655063]
28. Patsouris D, Li PP, Thapar D, Chapman J, Olefsky JM, Neels JG. Ablation of cd11c-positive cells normalizes insulin sensitivity in obese insulin resistant animals. *Cell metabolism*. 2008; 8:301–9. [PubMed: 18840360]
29. Di Gregorio GB, Yao-Borengasser A, Rasouli N, Varma V, Lu T, Miles LM, et al. Expression of cd68 and macrophage chemoattractant protein-1 genes in human adipose and muscle tissues: Association with cytokine expression, insulin resistance, and reduction by pioglitazone. *Diabetes*. 2005; 54:2305–13. [PubMed: 16046295]
30. Hou X, Wang O, Li Z, Mou H, Chen J, Deng B, et al. Upregulation of pancreatic derived factor (fam3b) expression in pancreatic beta-cells by mcp-1 (ccl2). *Molecular and cellular endocrinology*. 2011; 343:18–24. [PubMed: 21664946]
31. Curat CA, Wegner V, Sengenès C, Miranville A, Tonus C, Busse R, et al. Macrophages in human visceral adipose tissue: Increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia*. 2006; 49:744–7. [PubMed: 16496121]
32. 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; 116:1234–41. [PubMed: 17709633]
33. Britton KA, Fox CS. Perivascular adipose tissue and vascular disease. *Clinical lipidology*. 2011; 6:79–91. [PubMed: 21686058]
34. Chatterjee TK, Stoll LL, Denning GM, Harrelson A, Blomkalns AL, Idelman G, et al. Proinflammatory phenotype of perivascular adipocytes: Influence of high-fat feeding. *Circulation research*. 2009; 104:541–9. [PubMed: 19122178]
35. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *The American journal of clinical nutrition*. 2000; 71:885–92. [PubMed: 10731493]
36. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes care*. 2003; 26:372–9. [PubMed: 12547865]
37. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nature reviews Immunology*. 2011; 11:85–97.
38. Zimmet PZ, Collins VR, de Courten MP, Hodge AM, Collier GR, Dowse GK, et al. Is there a relationship between leptin and insulin sensitivity independent of obesity? A population-based study in the indian ocean nation of mauritius. Mauritius ncd study group. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*. 1998; 22:171–7.
39. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clinica chimica acta; international journal of clinical chemistry*. 2013; 417:80–4.
40. Minocci A, Savia G, Lucantoni R, Berselli ME, Tagliaferri M, Calo G, et al. Leptin plasma concentrations are dependent on body fat distribution in obese patients. *International journal of*

obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2000; 24:1139–44.

41. Park KG, Park KS, Kim MJ, Kim HS, Suh YS, Ahn JD, et al. Relationship between serum adiponectin and leptin concentrations and body fat distribution. *Diabetes research and clinical practice*. 2004; 63:135–42. [PubMed: 14739054]
42. Van Harmelen V, Reynisdottir S, Eriksson P, Thorne A, Hoffstedt J, Lonnqvist F, et al. Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes*. 1998; 47:913–7. [PubMed: 9604868]
43. Carbo N, Ribas V, Busquets S, Alvarez B, Lopez-Soriano FJ, Argiles JM. Short-term effects of leptin on skeletal muscle protein metabolism in the rat. *The Journal of nutritional biochemistry*. 2000; 11:431–5. [PubMed: 11091097]
44. Kohara K, Ochi M, Tabara Y, Nagai T, Igase M, Miki T. Leptin in sarcopenic visceral obesity: Possible link between adipocytes and myocytes. *PloS one*. 2011; 6:e24633. [PubMed: 21931785]

Highlights

- IMAT is a risk factor for insulin resistance, but the mechanism remains unclear.
- IMAT was positively correlated with MCP-1.
- IMAT might contribute to obesity-related diseases via affecting MCP-1 levels.

Figure 1. Subgroup comparisons between high adipokine groups and low adipokine groups
 Metabolic parameters such as fasting glucose, insulin and HOMA-IR in high adipokine groups and low adipokine groups. White bars represent the group with low MCP-1, leptin and adiponectin levels, respectively; black bars represent the subjects with high MCP-1, leptin and adiponectin levels, respectively
 MCP, monocyte chemoattractant protein-1; ADIPO, adiponectin; HOMA-IR, homeostatic model assessment of insulin resistance
 * $P < 0.05$, significant difference between high adipokine group and low adipokine group

Table 1

Anthropometric and metabolic characteristics of the study population

Variables	N=77
Age (year)	41.7 ± 10.9
Alcohol consumer	34 (44.2 %)
Calorie intake (kcal)	1500.2 ± 420.8
Energy expenditure (kcal)	304.0 ± 392.8
Metabolic parameters	
Systolic BP (mmHg)	128.7 ± 9.1
Diastolic BP (mmHg)	80.7 ± 8.5
Fasting glucose (mg/dL)	97.81 ± 9.14
Fasting insulin (μU/mL)	8.27 ± 5.03
HOMA-IR	2.03 ± 1.30
Adipokines	
MCP-1 (pg/mL)	98.8 ± 54.2
Leptin (ng/mL)	17.9 ± 8.2
Adiponectin (μg/mL)	2.8 ± 1.3
Anthropometric measurements	
Body mass index (kg/m ²)	28.4 ± 2.2
Waist circumference (cm)	90.5 ± 6.8
Body fat percentage (%)	39.0 ± 4.0
Total lean mass (kg)	39.5 ± 4.1
Abdominal fat	
Total abdominal fat area (cm ²)	387.8 ± 87.3
Visceral adipose tissue (cm ²)	104.7 ± 31.6
Subcutaneous adipose tissue (cm ²)	283.1 ± 77.6
Thigh cross-sectional area	
Total thigh muscle area (cm ²)	106.8 ± 14.5
High-density muscle (cm ²)	91.8 ± 15.6
Low-density muscle (cm ²)	15.1 ± 5.0
Intermuscular adipose tissue (cm ²)	5.8 ± 3.6

Data are expressed as means ± SD or number (percentage)

BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; MCP-1, monocyte chemoattractant protein-1

Table 2

Pearson correlation coefficient (r) among MCP-1, Leptin, adiponectin, metabolic variables, and body composition

	MCP-1			Leptin			Adiponectin		
	r	P		r	P		r	P	
Factors for diet and physical activity									
Calorie intake	0.093	0.422		-0.078	0.502		0.027	0.814	
Energy expenditure	0.065	0.571		0.063	0.585		-0.030	0.793	
Anthropometric measurements									
Body mass index	0.017	0.886		0.411	<0.001 [*]		-0.090	0.435	
Waist circumference	0.132	0.251		0.322	0.004 [*]		-0.030	0.798	
Body fat percentage	-0.007	0.955		0.480	<0.001 [*]		-0.030	0.798	
Total lean mass	0.158	0.174		0.093	0.426		-0.067	0.567	
Abdominal fat									
Total abdominal fat area	0.077	0.505		0.479	<0.001 [*]		-0.112	0.333	
Visceral adipose tissue	0.204	0.076		0.213	0.063		-0.064	0.582	
Subcutaneous adipose tissue	0.004	0.972		0.452	<0.001 [*]		-0.100	0.388	
Thigh cross-sectional area									
Total thigh muscle area	-0.114	0.328		-0.127	0.275		-0.150	0.195	
High-density muscle	-0.215	0.060		-0.131	0.253		-0.147	0.201	
Low-density muscle	0.355	0.002 [*]		0.005	0.968		0.024	0.839	
Intermuscular adipose tissue	0.483	<0.001 [*]		0.222	0.052		0.079	0.495	
Metabolic parameters									
Systolic BP	0.101	0.381		-0.029	0.804		0.009	0.939	
Diastolic BP	0.106	0.357		-0.102	0.378		0.063	0.587	
Fasting glucose	-0.080	0.490		-0.042	0.716		-0.170	0.140	
Fasting insulin	0.098	0.396		0.403	<0.001 [*]		-0.192	0.095	
HOMA-IR	0.072	0.535		0.360	0.001 [*]		-0.202	0.078	

r indicates Pearson correlation coefficient; MCP-1, monocyte chemoattractant protein -1; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance

^{*} P < 0.05

Table 3
Multivariate linear regression analysis of adiposity measures with MCP-1, Leptin and Adiponectin

	MCP-1		Leptin		Adiponectin	
	β	P	β	P	β	P
Model 1						
Age	0.153	0.164	-0.189	0.127	0.002*	0.990
Height	0.227	0.041*	0.046	0.707	-0.119	0.351
Intermuscular adipose tissue	0.476	<0.001*	0.223	0.049*	0.081	0.484
Model 2						
Age	0.045	0.736	-0.268	0.048*	0.005*	0.976
Height	0.302	0.022*	0.035	0.785	-0.058	0.706
Intermuscular adipose tissue	0.433	0.001*	-0.051	0.686	0.080	0.588
Visceral adipose tissue	0.050	0.675	0.248	0.041*	-0.071	0.615
Subcutaneous adipose tissue	-0.130	0.254	0.390	0.001*	-0.078	0.565
High-density muscle	-0.134	0.357	-0.317	0.031*	-0.072	0.673

Model 1 was adjusted for age and height whereas model 2 was adjusted for age, height and body composition metrics.

MCP-1, monocyte chemoattractant protein-1

* P < 0.05