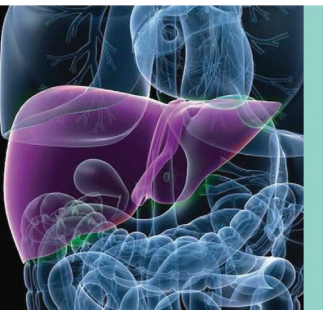

Nonalcoholic Fatty Liver Disease: The Role of Visceral Adipose Tissue

Courtney L. Hanlon, M.D., M.S.[*], *and Liyun Yuan, M.D., Ph.D.*[*,†]

Abdominal obesity describes multiple fat compartments including visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), each of which carry significantly different metabolic risk. SAT is the largest adipose tissue depot and serves largely as protective lipid storage. When this storage capacity is exceeded, fat deposits outside of subcutaneous tissue such as into visceral tissue, the epicardium, and the liver. These ectopic fats promote insulin resistance, local inflammation, and atherogenic changes.[1-4] VAT in particular is associated with cardiovascular risk, insulin resistance, metabolic unhealthy obesity, and hepatic steatosis.[1,2] The distribution of lipids among SAT, VAT, and liver tissue has been implicated in metabolic hemostasis and progression of nonalcoholic fatty liver disease (NAFLD).[1,4,5]

Current clinical tools for estimating fat do not differentiate between these fat depots, and adipose reduction therapy is still aimed at overall weight loss rather than tissue-targeted therapy. The goal of this review is to describe the role of VAT in the development of NAFLD, clinical tools aimed at estimating VAT, and future therapies being evaluated for NAFLD treatment via VAT reduction.

PATHOGENESIS OF VAT IN NAFLD PROGRESSION

VAT is a well-demonstrated independent risk factor for type 2 diabetes as well as for cardiovascular and metabolic disease via its important role in atherogenic dyslipidemia, insulin resistance, pro-inflammatory states, and elevated blood pressure[1-4] (Fig. 1).[3] Visceral fat releases increased free fatty acids (FFAs) and triglycerides into the circulation and can cause inhibition of glucose uptake, glucose oxidation, and glycogen synthesis via several mechanisms as seen in Fig. 2. Increased FFAs to the liver via the portal vein also act as ligands for Toll-like receptor (TLR) 4 and induce cytokine production, thereby contributing to inflammation pathways associated with NAFLD.[5,6]

Abbreviations: BMI, body mass index; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; FFA, free fatty acid; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; SAT, subcutaneous adipose tissue; TLR, Toll-like receptor; TZD, thiazolidinediones; VAT, visceral adipose tissue; WC, waist circumference.

From the [*]Department of Medicine, University of Southern California, Keck School of Medicine of USC, Los Angeles, CA; and [†]Division of Gastrointestinal and Liver Diseases, University of Southern California, Keck Hospital of USC, Los Angeles, CA.

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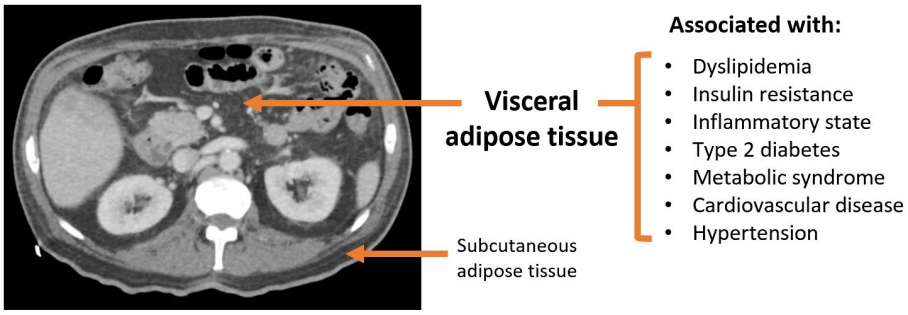

FIG 1 Cross-section of abdomen with visceral versus subcutaneous fat.

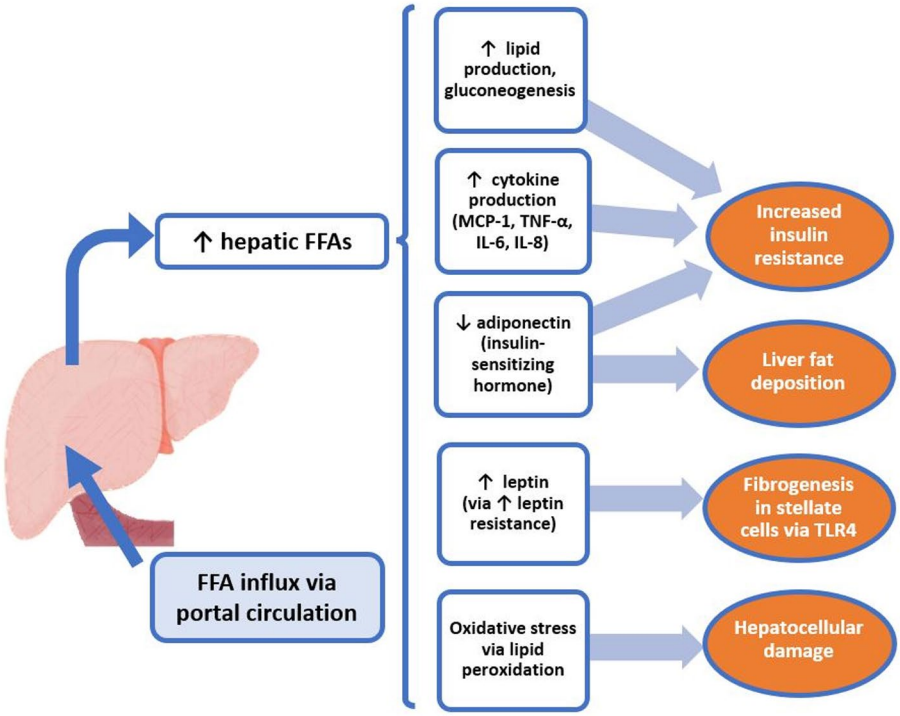

FIG 2 NAFLD as a function of impaired lipid metabolism.

VAT-associated increases in immune cell activity and markers of inflammation within liver tissue can lead to altered production of adiponectin, a key protein in insulin sensitivity regulation.[4] This impairment leads to lipotoxic accumulation of fatty acids directly into the liver through portal circulation, known as ectopic fat storage, reducing hepatic insulin clearance and increasing gluconeogenesis, dyslipidemia, and hepatic fat deposition (Fig. 3).[4,5,7]

CLINICAL MEASUREMENTS OF VISCERAL FAT

Despite its known limitations, body mass index (BMI) is still the most widely used metric for obesity and metabolic-related risk. However, BMI alone is insufficient to properly assess health risk associated with increased adiposity, does not distinguish between fat mass and lean mass, and can have extreme variation among individuals of the same weight with different levels of visceral fat.[6,8,9] More focused measures of adiposity and body composition are needed to capture individual health risk. Radiologic assessment of body composition, such as through computed tomography (CT), magnetic resonance imaging (MRI), or dual-energy x-ray absorptiometry (DEXA) has allowed for improved calculation of VAT and has been validated against direct metrics such as histology.[10,11] However, these modalities are costly and typically reserved for research purposes; as such,

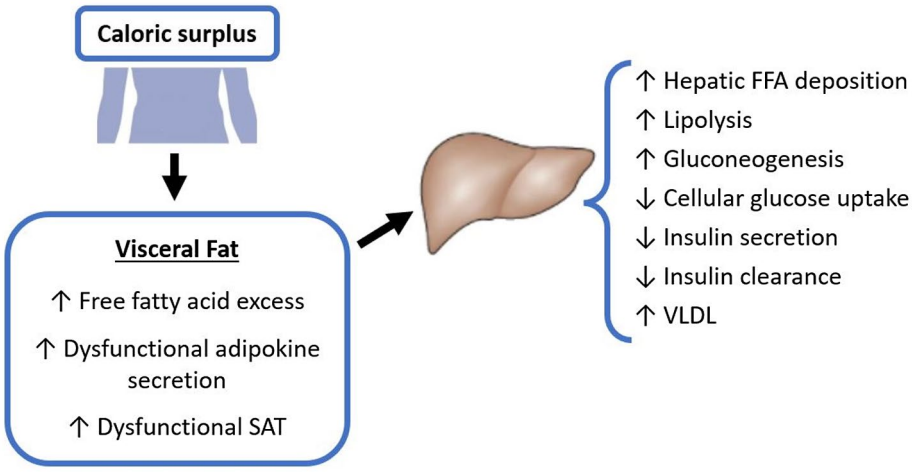

FIG 3 Role of VAT in dysfunctional lipid regulation.

TABLE 1. ANTHROPOMETRIC MEASURES OF VISCERAL ADIPOSE TISSUE FOR USE IN NAFLD

Anthropometric Marker	Abbreviation	Advantages	Disadvantages	Correlation With VAT
Body mass index	BMI	Large amount of evidence, simple to calculate	Low correlation to VAT within certain subgroups and overall	0.67-0.84
Waist circumference	WC	Well documented in literature, use in clinic	Variability of measurement location without consensus, WC alone cannot distinguish SAT from VAT	0.50-0.87
Waist-to-height ratio	WHtR	Index of central obesity, well studied, simple to calculate	Not superior to WC alone	0.52-0.81
Waist-to-hip ratio	WHR	Well studied, easy to use in clinic setting	Not superior to WC alone	0.67-0.71
Neck circumference	NC	Easy to obtain measurement	Not well documented in literature	0.63-0.82
Homeostatic model of insulin resistance	HOMA-IR	Established association with metabolic dysfunction	Requires less common serologies (fasting insulin, fasting glucose)	0.42-0.69
Visceral adiposity index	VAI	Effective marker for stratifying obesity phenotypes, gender-specific	Not yet widely validated in NAFLD	–
Lipid accumulation product	LAp	Stratification of obesity phenotypes, established screening tool for metabolic syndrome, gender-specific	Not yet widely validated in NAFLD	–
Product of triglycerides and glucose	TyG	Stratification of diabetes versus prediabetes and metabolic risk	Not yet widely validated in NAFLD	–

surrogate anthropometric measures have been developed (Table 1).

Waist circumference (WC) is predictive of increased VAT among people with the same BMI, and has been shown to be more strongly associated with amount of VAT than waist-to-hip ratio.[7,12] When WC is paired with triglyceride levels, it has been shown to be predictive of increased VAT levels and metabolic syndrome with approximately 80% probability.[2] Additionally, measured hyperinsulinemia and elevated apolipoprotein B concentrations have been closely related to VAT accumulation, suggesting that a combination of anthropometric and serologic measures more accurately captures VAT and associated risk of NAFLD.[13] Visceral adiposity index (VAI), a model computed by both anthropometric (BMI and WC) and laboratory parameters such as triglycerides and high-density lipoprotein cholesterol, serves as an indicator of visceral fat function associated with insulin resistance and cardiometabolic risk.[14] VAI has been implicated as a valuable predictor of NAFLD; other potential indices of insulin resistance such as lipid accumulation product (LAp) and product of triglycerides and glucose (tyG) are reliable indices to discriminate between prediabetes and diabetes among the general population.[14] These markers also reflect visceral fat dysfunction and metabolic unhealthy obesity. As research in this area continues, measures of abdominal obesity and markers of

TABLE 2. NOVEL THERAPEUTIC STRATEGIES TO REDUCE VISCERAL ADIPOSE TISSUE FOR USE IN NAFLD

Novel Therapeutic Target	Mechanism of action
Adiponectin replacement	Increase fatty acid oxidation, reduce oxidative stress and liver fibrosis
Leptin replacement	Promote lipid mobilization, reduce liver fat deposition
TZDs (PPAR-γ agonist)	Increase circulating adiponectin levels, regulate inflammation, improve fibrosis
SGLT-2 inhibitor	Reduce ectopic fat, reverse hepatic fibrosis

metabolic syndrome associated with increased VAT could refine NAFLD risk assessment beyond current methods used in clinical practice.

TARGETED TREATMENT TO IMPROVE VISCERAL FAT FUNCTION

There is a critical need for effective medical therapies for patients with NAFLD. Weight loss and regular exercise combined with a healthy diet is strongly associated with VAT reduction and improvement of hepatic steatosis independent of age, sex, and ethnicity.[3,4,8] In addition to behavioral changes, therapeutic options to reduce VAT beyond nutritional and activity habits are of great interest to NAFLD treatment researchers (Table 2). Promising targets include adiponectin and leptin, hormones released by visceral adipose tissue that are strongly inversely associated with risk of metabolic syndrome, body composition, and hepatic dysfunction. Increasing levels of these adipose mediators are associated with improvement of visceral fat function and hindrance of NAFLD development and progression.[15] Peroxisome proliferator-activated receptors (PPAR)-γ agonists, known as thiazolidinediones (TZDs), reduce fat accumulation in visceral depot and liver and increase fat storage of SAT. This is mediated by increased release of adiponectin, thereby alleviating inflammatory cascades within visceral fat via PPAR-γ activation.[16] A systemic meta-analysis shows that pioglitazone 30 mg daily or 45 mg daily improves NAFLD activity scores and fibrosis in both diabetic and non-diabetic patients.[17] However, side effects of TZDs, including weight gain, fluid retention, and risk of bone fracture, have greatly limited their tolerance.

Ipragliflozin, a sodium-glucose co-transporter-2 inhibitor, has also been shown to reduce epicardial fat in both obese and non-obese patients with type 2 diabetes; further studies should clarify whether a similar effect is seen in visceral liver fat.[18] Newer therapeutic targets aimed at improving visceral fat function and reducing VAT volume in conjugation of lifestyle modification may improve metabolic outcome and halt progression of NAFLD and NASH.

CONCLUSION

Anatomically adjacent to the liver, VAT plays an important role in NAFLD pathogenesis via its diabetogenic, atherogenic, and pro-inflammatory functions. Many anthropometric metrics and insulin-resistance markers are being studied to gauge VAT function, with the goal of predicting metabolic risk and NAFLD surveillance. There is significant unmet need to improve accuracy of current clinical models and develop effective therapies that enhance VAT function as a target for NAFLD treatment.

AUTHOR CONTRIBUTIONS

Concept and Design: C.H., L.Y. Drafting and Revision of Manuscript: C.H., L.Y.

CORRESPONDENCE

Liyun Yuan, M.D., Ph.D., Division of Gastrointestinal and Liver Diseases, Keck School of Medicine at University of Southern California, 1450 San Pablo St HC4 Ste 3000, Los Angeles CA 90033. E-mail: lyuan@med.usc.edu

REFERENCES

1) Neeland IJ, Ross R, Després J-P, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol 2019;7:715-725.

2) Lemieux I, Poirier P, Bergeron J, et al. Hypertriglyceridemic waist: A useful screening phenotype in preventive cardiology? Can J Cardiol 2007;23:23B-31B.

3) Expert Panel on Detection E. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-2497.

4) McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes 2002;51:7-18.

5) Seppälä-Lindroos A, Vehkavaara S, Häkkinen A-M, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023-3028.

6) Tchernof A, Després J-P. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013;93:359-404.

7) Snijder M, Van Dam R, Visser M, Seidell J. What aspects of body fat are particularly hazardous and how do we measure them? Int J Epidemiol 2006;35:83-92.

8) Neeland IJ, Poirier P, Després J-P. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation 2018;137:1391-1406.

9) Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. Nat Rev Endocrinol 2020;16:177-189.

10) Linge J, Borga M, West J, et al. Body composition profiling in the UK Biobank Imaging Study. Obesity 2018;26:1785-1795.

11) Kaul S, Rothney MP, Peters DM, et al. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity 2012;20:1313-1318.

12) Nazare J-A, Smith J, Borel A-L, et al. Usefulness of measuring both body mass index and waist circumference for the estimation of visceral adiposity and related cardiometabolic risk profile (from the INSPIRE ME IAA study). Am J Cardiol 2015;115:307-315.

13) Lemieux S, Prud'Homme D, Tremblay A, Bouchard C, Despres J. Anthropometric correlates to changes in visceral adipose tissue over 7 years in women. Int J Obes Relat Metab Disord 1996;20:618-624.

14) Ahn N, Baumeister SE, Amann U, et al. Visceral adiposity index (VAI), lipid accumulation product (LAP), and product of triglycerides and glucose (TyG) to discriminate prediabetes and diabetes. Sci Rep 2019;9:1-11.

15) Boutari C, Mantzoros CS. Adiponectin and leptin in the diagnosis and therapy of NAFLD. Metab-Clin Exp 2020;103:154028.

16) Polyzos SA, Mantzoros CS. Adiponectin as a target for the treatment of nonalcoholic steatohepatitis with thiazolidinediones: a systematic review. Metabolism 2016;65:1297-1306.

17) Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med 2017;177:633-640.

18) Fukuda T, Bouchi R, Terashima M, et al. Ipragliflozin reduces epicardial fat accumulation in non-obese type 2 diabetic patients with visceral obesity: a pilot study. Diabetes Therapy 2017;8:851-861.