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Adipose Tissue, Can It Be Named As A Lipostat?

T. Atma Ram, Mada Medical College, Chennai,

P. Saraswathi, Manopriya, T and Dhastagir Sultan Sheriff,
Anna Medical College, Mauritius.
Corresponding author:drdsheriff@gmail.com

Abstract
Adipose tissue is lipid storage organ. Lipogenesis and Lipolysis plays an important role in its metabolism. The triglycerides either carried as chylomicrons or endogenous triglycerides packaged as Very Low Density Lipoprotein (VLDL) are acted upon by the enzyme lipoprotein lipase to release fatty acids which are taken by the AT and stored as triglycerides. The uptake and release of fatty acids by the adipose tissue is regulated by LPL and the vasculature of AT.

Key words:*Adipose tissue, lipoprotein lipase (LPL), Chylomicrons, VLDL*

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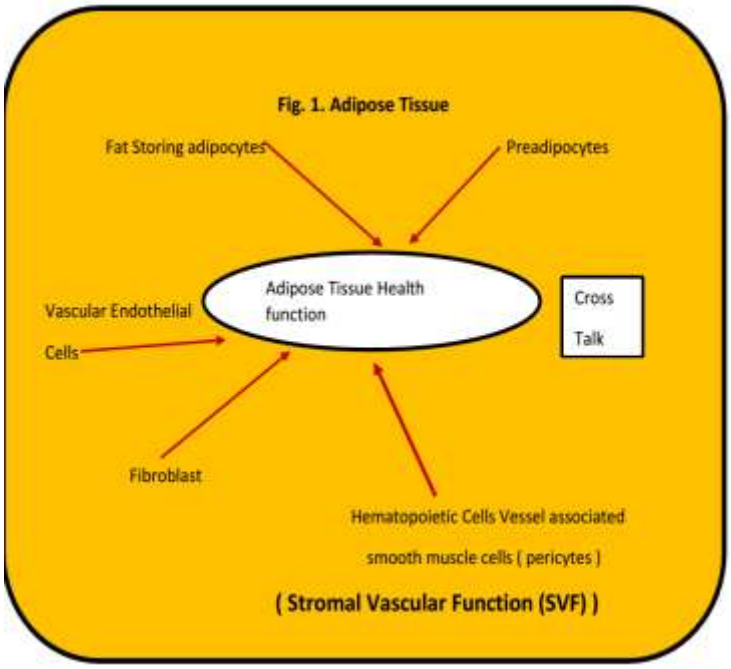
I. Introduction:

Adipose tissue (AT) is one of the important organs that balances whole body energy status. Adipose tissue maintains the balance by regulating storage and utilization of Triglyceride stores. The balancing act of AT helps to protect tissues from lipid overload and lipo-toxicity.

Continued positive calorie intake leads to expansion of AT until it reaches it threshold of storage beyond which AT capacity to store lipid decreases, results in leakage from AT and causes lipid accumulation in peripheral organs leading deterioration of metabolic health.

The deleterious effects lipid accumulation are illustrated in cases with lipo-dystrophy and animal models that lack adequate amounts of AT. The metabolic abnormalities expressed are ectopic lipid deposition, hypertriglyceridemia, insulin resistance (IR) and probably type 2 Diabetes Mellitus (T2DM).



Endothelial cells (ECs) are squamous cells that make up inner lining of all vessels,that regulate multiple physiological processes, acting as a barrier between organs and the blood, overseeing the delivery of nutrients and oxygen to the underlying tissue. ECs are heterogenous cell population with distinct morphological and functional characteristics according to vessel size, anatomical location and local metabolic demand. Microvessels or capillaries are lined by thin layer of ECs encased by a supporting medium of pericytes allowing them deliver gases, fluids and macromolecules to the parenchyma.

Transport across the microvascular epithelium differ from tissues and capillary types. There are two transport, paracellular and transcellular. Paracellular transport is unregulated movement of macromolecules between ECs and the underlying tissue. Transcellular transport is regulated by transporters though the ECs. Vascular function in these systems is tightly regulated. AT has a continuous non-leaky AT vasculature helps to regulate the quantity and types of macromolecules taken up stored and released by AT.

Highly vascularized AT has each adipocyte lie adjacent to each other having one micro-vessel in the lean status. ECs help adipocyte to cross talk to enable continuous regulation of AT lipid dynamics in response to changes in systemic energy levels, ensuring

1. Adequate storage and release
2. Impact on the capacity of the AT to expand during weight gain and obesity.

AT Vasculature

AT vasculature helps to selectively deliver nutrients for energy usage and storage acting as a differentiation niche and regulating hyperplastic adipose tissue expansion and release of adipokines and hydrolyzed fatty acids via the vasculature possibly through the lymphatics. In other words like liver AT acts as a buffer for whole body fed and fasting lipid fluxes. It is reported that administration of C^{14} labeled TAG, 34g of lipid is fluxed through AT of a stable weight individual .

Circulating fatty acid uptake at AT after hydrolysis of triglycerides with capillary lipoprotein lipase (LPL) anchored to the luminal side of AT ECs, fatty acids are transported to the endothelial cells. ECs don't express LPL but express LPL-anchoring protein, glycosyl phosphatidyl inositol anchored to HDL binding protein1 (GPIHBP1).

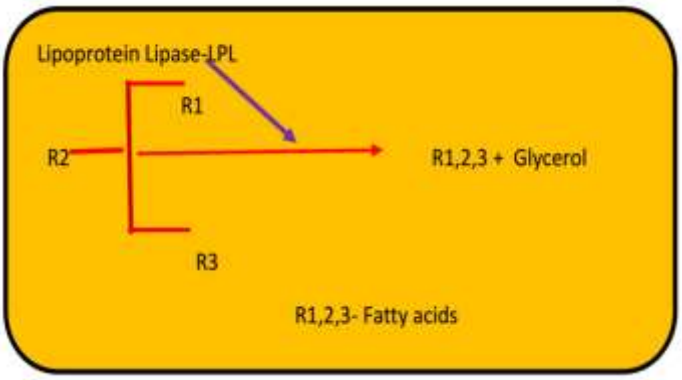


Fig.2. Lipoprotein Lipase action- heparin releasable, apoprotein CII activating enzyme

The synthesis and release of LPL by adipocyte cooperate with endothelial expression of GPIHBP1 helps paracrine cross talk for endothelial uptake of FA uptake. LPL promoted release of fatty acids are partitioned to AT in the fed state and towards skeletal muscle during fasting state. Angiopoietin like protein (ANGPTIs) regulate local LPL activity. ANGPTL4 is upregulated in AT upon fasting and down-regulated LPL during fasted state by limiting Fatty acid uptake by AT. ANGPTL3 and 8 cooperate to limit FA uptake by muscle in the fed state. ANGPTL 8 released by AT and liver upon feeding suppresses LPL activity promoting FA uptake by AT

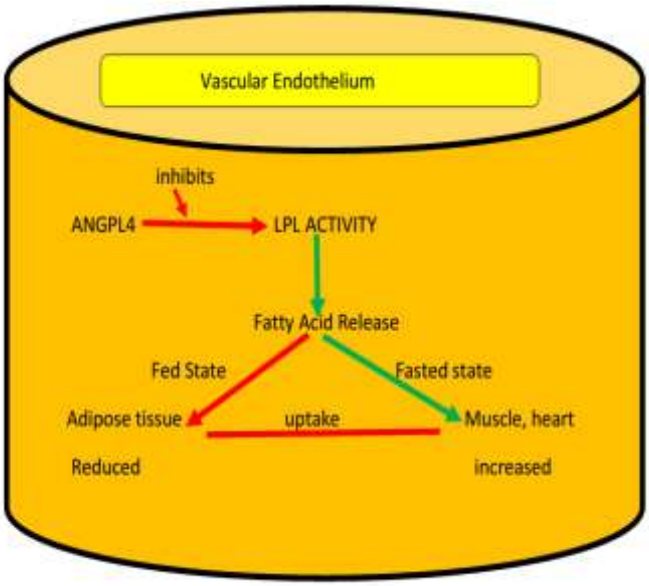


Fig.3. Inhibition of LPL activity by ANGPL4

ANGPL4- Angiopoietin like protein 4; FA- fatty acid; LPL-lipoprotein lipase

In the fed state, ANGPL8 binds to ANGPL4 during the fed state, stimulates LPL activity and the released fatty acids are stored in the AT.

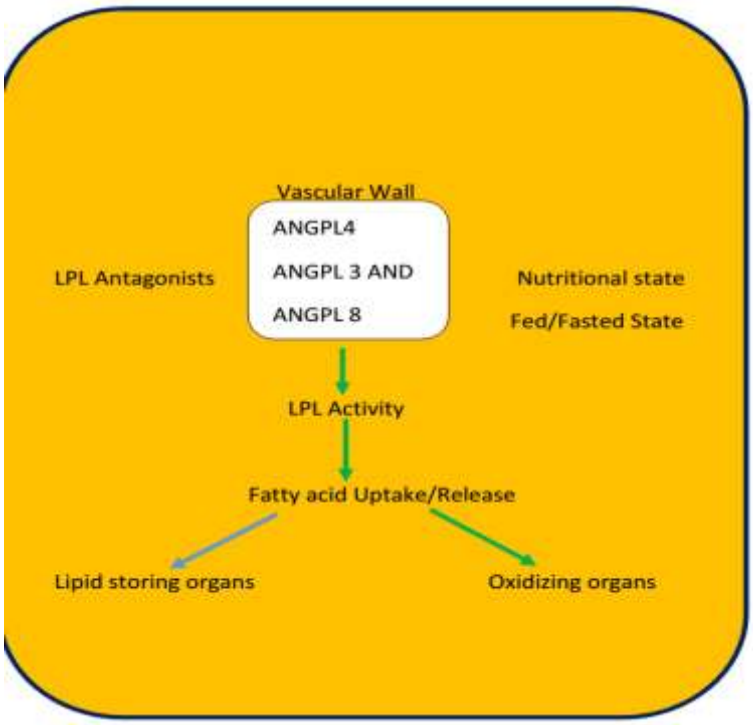


Fig. 4 Angiopoietin like Proteins role in Fatty acid uptake in adipose tissue/skeletal/heart muscle

ANGPL- angiopoietin like LPL- lipoprotein lipase activity

Mutations in LPL with inactivating result cause early onset of hypertriglyceridemia and gain of function ones results in a protective phenotype against metabolic disease. Mutations in in LPL interacting proteins (GPIHBP 1 and ANGPTLs) cause hyperlipidemia.

Therefore, LPL activity and fatty acid uptake in AT regulate and maintain metabolic balance and metabolic health.

Vesicle mediated transport through the adipose tissue epithelium involves capillary endothelial cells. These ECs have great numbers if vesicles on the surface to transport small volumes of plasma and interstitial fluid across the endothelial barrier via vesicular transcytosis.

Adipocyte ECs are rich in caveolae concentrated around sphingolipid and cholesterol domain within the endothelial surface.

Caveolins 1 and 2 and cavins 1 and 2 are the main proteins that regulate adipocyte Caveolar formation. Studies in knockout mice have shown that a functioning caveolae play an important role in the development and functions of AT.

The recent findings of exchange of cargo and plasma membrane fragments between ECs and adipocytes show that Caveolae-type vesicles may mediate cross talk between ECs and adipocyte within the tissue. Caveolin containing vesicles and endothelial cells play an important role in Adipocyte function. The EC-derived extracellular vesicles is regulated by glucagon, providing possible evidence to show EC-adipocyte cross talk is regulated by hormones.

ECs secrete few fat acid binding proteins (FABP) including C 36, which seem to play a role in the ferrying of molecules between ECs and Adipocytes. Very low density lipoprotein receptor (VLDLR) is implicated in postprandial uptake peripheral triglyceride in adipose tissue and skeletal muscle. VLDLR is also reported to interact with LpL to promote fatty acid release and vesicular transcytosis of whole lipoproteins to the parenchymal cells. Therefore, further studies are required to fully understand the cross talk and adipose tissue-EC axis along with LpL's role in regulating adipose tissue lipolysis and lipogenesis.

If liver is considered as a glucostat with glucose-6-phosphatase acting as a regulator, adipose tissue can be called as a Lipostat with LPL acting as a regulator.

References:

[1]. Frayn KN. Adipose tissue as a buffer for daily lipid flux. Diabetologia 2002;45(9):1201-1210.
[2]. Arner P, Bernard S, Salehpour M, et al. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature. 2011; 478(7367):110-113.
[3]. Arner P, Bernard S, Appelsved L, et al. Adipose lipid turnover and long-term changes in body weight. Nat Med. 2019;25(9):1385-1389.
[4]. Yucel N, Arany Z. Fat, obesity, and the endothelium.CurrOpin Physiol. 2019;12:44-50.
[5]. Mann JP, Savage DB. What lipodystrophies teach us about the metabolic syndrome.JClin Invest. 2019;129(10):4009-4021.
[6]. Krüger-Genge A, Blocki A, Franke RP, Jung F. Vascular endothelial cell biology: An update.Int J Mol Sci. 2019;20(18):1–22.
[7]. van Dijk CG, Nieuweboer FE, Pei JY, et al. The complex mural cell: pericyte function in health and disease.Int J Cardiol. 2015;190: 75-89.
[8]. Komarova Y, Malik AB. Regulation of endothelial permeability via paracellular and transcellular transport pathways. Annu Rev Physiol. 2010;72(1):463-493.
[9]. Hasan SS, Fischer A. The endothelium: An active regulator of lipid and glucose homeostasis.Trends Cell Biol. 2020;31(1):37-49.
[10]. Graupera M, Claret M. Endothelial cells: New players in obesity and related metabolic disorders. Trends Endocrinol Metab. 2018;29(11): 781-794
[11]. Wu SA, Kersten S, Qi L. Lipoprotein lipase and its regulators: An unfolding story.Trends Endocrinol Metab. 2021;32(1):48-61.
[12]. Beigneux AP, Davies BS, Gin P, et al. Glycosyl phosphatidyl inositol anchored high-density lipoprotein-binding protein 1 plays a critical role in the lipolytic processing of chylomicrons. Cell Metab. 2007; 5(4):279-291.
[13]. Young SG, Fong LG, Beigneux AP, et al. GPIHBP1 and lipoprotein lipase, partners in plasma triglyceride metabolism. Cell Metab. 2019; 30(1):51-65.
[14]. Kim I, Kim HG, Kim H, et al. Hepatic expression, synthesis and secretion of a novel fibrinogen/angiopoietin-related protein that prevents endothelial-cell apoptosis. Biochem J. 2000;346(Pt 3):603-610.
[15]. Chen YQ, Pottanat TG, Siegel RW, et al. Angiopoietin-like protein 8 differentially regulates ANGPTL3 and ANGPTL4 during postprandial partitioning of fatty acids.J Lipid Res. 2020;61(8):1203-1220.
[16]. Oldoni F, Cheng H, Banfi S, Gusarova V, Cohen JC, Hobbs HH. ANGPTL8 has both endocrine and autocrine effects on substrate utilization. IJC Insight. 2020;5(17):e138777.
[17]. Al-Bustan SA, Al-Serri A, Alnaqeeb MA, Annice BG, Mojiminiyi O. Genetic association of LPL rs1121923 and rs258 with plasma TG and VLDL levels. Sci Rep. 2019;9(1):5572–5582.
[18]. Romeo S, Yin W, Kozlitina J, et al. Rare loss-of-function mutations in ANGPTL family members contribute to plasma triglyceride levels in humans.JClin Invest. 2009;119(1):70-79.
[19]. Rippe B, Rosengren BI, Carlsson O, Venturoli D. Transendothelial transport: The vesicle controversy. J Vasc Res. 2002;39(5):375-390.
[20]. Michel CC, Curry FE. Microvascular permeability.Physiol Rev. 1999; 79(3):703-761.
[21]. Debbage PL, Sölder E, Seidl S, et al. Intravital lectin perfusion analysis of vascular permeability in human micro- and macro- blood vessels. Histochem Cell Biol. 2001;116(4):349-359.
[22]. Filippini A, D'Alessio A. Caveolae and lipid rafts in endothelium: Valuable organelles for multiple functions. Biomolecules. 2020;10(9): 1218.1218–1234.
[23]. Frank PG, Pavlides S, Lisanti MP. Caveolae and transcytosis in endothelial cells: Role in atherosclerosis. Cell Tissue Res. 2009;335(1): 41-47.
[24]. Haddad D, Al Madhoun A, Nizam R, Al-Mulla F. Role of caveolin-1 in diabetes and its complications. Oxid Med Cell Longev. 2020;2020: 9761539.
[25]. Ramírez CM, Zhang X, Bandyopadhyay C, et al. Caveolin-1 regulates atherogenesis by attenuating low-density lipoprotein transcytosis and vascular inflammation independently of endothelial nitric oxide synthase activation.Circulation. 2019;140(3):225-239.

[26]. Hansen CG, Shvets E, Howard G, Riento K, Nichols BJ. Deletion of cavin genes reveals tissue-specific mechanisms for morphogenesis of endothelial caveolae. Nat Commun. 2013;4(1):1831–1844.
[27]. Razani B, Combs TP, Wang XB, et al. Caveolin-1-deficient mice are lean, resistant to diet-induced obesity, and show hypertriglyceridemia with adipocyte abnormalities. J Biol Chem. 2002; 277(10):8635-8647.
[28]. Liu L. Lessons from cavin-1 deficiency.BiochemSoc Trans. global caveolin-1 knockout mice.JExp Med. 2007;204(10):2373-2382.
[29]. Briand N, Le Lay S, Sessa WC, Ferré P, Dugail I. Distinct roles of endothelial and adipocyte caveolin-1 in macrophage infiltration and adipose tissue metabolic activity. Diabetes. 2011;60(2):448-453.
[30]. Crewe C, Joffin N, Rutkowski JM, et al. An endothelial-to-adipocyte extracellular vesicle axis governed by metabolic state. Cell. 2018; 175(3):695-708.e13.
[31]. 43. Yazdani S, Jaldin-Fincati JR, Pereira RVS, Klip A. Endothelial cell barriers: Transport of molecules between blood and tissues. Traffic. 2019;20(6):390-403.
[32]. Son N-H, Basu D, Samovski D, et al. Endothelial cell CD36 optimizes tissue fatty acid uptake.JClin Invest. 2018;128(10):4329-4342.
[33]. Hao J-W, Wang J, Guo H, et al. CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis.NatCommun. 2020; 11(1):4765–4781.
[34]. Wyne KL, Pathak K, Seabra MC, Hobbs HH. Expression of the VLDL receptor in endothelial cells. ArteriosclerThrombVasc Biol. 1996; 16(3):407-415.
[35]. Goudriaan JR, Espirito Santo SM, Voshol PJ, et al. The VLDL receptor plays a major role in chylomicron metabolism by enhancing LPL mediated triglyceride hydrolysis.J Lipid Res. 2004;45(8):1475-1481.