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CHAPTER

Ectopic Fat: Pathophysiology and Consequences

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ABSTRACT

Ectopic fat refers to the accumulation of triglycerides within nonadipose tissues, such as the liver, skeletal muscle, heart, and pancreas, which normally contain minimal fat deposits. This ectopic fat deposition can impair cellular functions and organ performance, and it is closely associated with insulin resistance. Various methods are available to quantify ectopic fat, including invasive techniques like histomorphology and chemical analyses, as well as noninvasive imaging methods such as ultrasound, MRI, CT scan, and MRS scan.

In the context of cardiac health, ectopic fat accumulation around the heart or within the pericardium can lead to obesity-related cardiomyopathy. Lipid oversupply to cardiomyocytes causes mitochondrial dysfunction, inflammation, and compromised cardiac function, ultimately contributing to heart failure. Understanding the impact of obesity on cardiac metabolism is crucial for preventing heart disease and developing targeted metabolic therapies.

Epicardial adipose tissue (EAT) and perivascular adipose tissue (PVAT) have distinct roles in cardiac health. EAT provides mechanical support and serves as an energy depot for the myocardium, while PVAT exhibits both anti-inflammatory and proinflammatory characteristics, depending on obesity status. Both tissues have the potential to serve as markers of cardiometabolic risk and therapeutic targets.

In the context of hepatic health, ectopic fat accumulation in the liver can lead to nonalcoholic fatty liver disease (NAFLD) and its progressive stages, including nonalcoholic steatohepatitis (NASH) and cirrhosis. Insulin resistance and altered glucose and fat metabolism contribute to hepatic steatosis. NAFLD is closely linked to metabolic syndrome and affects diabetic, obese, and dyslipidemic populations. Lifestyle interventions and certain medications have shown promise in reducing hepatic fat and improving glycemic control in NAFLD patients.

Skeletal muscle adiposity, including intermuscular and intramuscular fat, correlates with insulin resistance and can impact cardiometabolic risk. Renal lipid accumulation and lipotoxicity play a crucial role in the development and progression of chronic kidney disease (CKD). Pancreatic fat accumulation can lead to nonalcoholic fatty pancreatic steatosis (NAFPD), which may contribute to inflammation and β-cell dysfunction.

The role of ectopic fat in type 2 diabetes mellitus (T2DM) is complex and remains debated. Some evidence suggests that ectopic fat causes organ-specific insulin resistance, while others demonstrate a more nuanced relationship between fat distribution and insulin sensitivity.

The mineralocorticoid receptor (MR) is involved in adipocyte differentiation and adipocyte dysfunction in obesity. Hepatokines, hormone-like proteins secreted by hepatocytes, play a central role in metabolism, and their altered secretion in NAFLD can lead to systemic metabolic dysregulation.

Ectopic fat accumulation has profound implications for various organ systems, including the heart, liver, skeletal muscle, pancreas, and kidneys. Understanding the mechanisms underlying ectopic fat accumulation and its metabolic consequences is essential for developing targeted therapies to mitigate the adverse effects of obesity-related ectopic fat deposition and associated diseases. Further research is needed to explore potential therapeutic strategies and their impact on reducing the prevalence of obesity-related cardiovascular and metabolic disorders.

INTRODUCTION

Ectopic fat, defined as the deposition of triglycerides (TGs) within nonadipose tissues (like liver, skeletal muscle, heart, and pancreas), interferes with cellular and organ function and can cause insulin resistance.

QUANTIFICATION OF ECTOPIC FAT

Ectopic fat can be assessed invasively through histomorphology or chemical analysis of tissue biopsies. However, noninvasive methods like ultrasound, MRI, CT scan, and MRS scan offer advantages like intact regions of interest, large tissue volume examination, and repeated measurements during interventions.

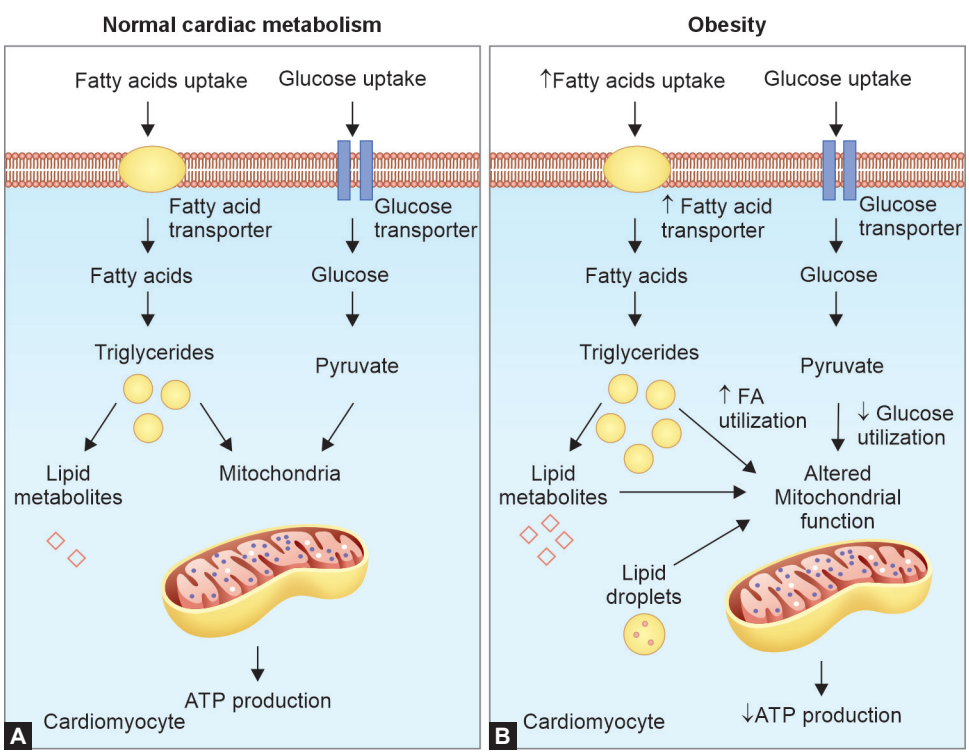
ECTOPIC FAT AND DISEASE CONDITIONS

Ectopic Fat in the Cardiac Health

Cardiac fat accumulates around the heart (pericardial fat) or within the pericardium (epicardial fat), with varying capacities and metabolic effects. Cardiomyopathy brought on by obesity changes the energetics and metabolism of the heart, causing cardiac dysfunction. Over 70% of the adenosine triphosphate (ATP) needed by the heart is produced by fatty acid oxidation. Only a minor quantity of TG is present in the heart due to the close coupling between the oxidation and absorption of fatty acids. When the rate of fatty acid intake exceeds that of oxidation, lipids build up in the cardiomyocytes, which can contribute to cardiac fat accumulation, causing mitochondrial dysfunction, reactive oxygen species, inflammation, and compromised cardiac function. Insulin resistance and impaired glucose utilization further increase fatty acid uptake and accumulation in the myocardium **(Figs. 1A and B)**.

Future Implications

Understanding how obesity affects cardiac metabolism and function is crucial for preventing cardiovascular-related morbidity and mortality. Advanced imaging techniques can help study the relationship between adiposity, cardiac fat depots, cardiac metabolism, and the risk of obesity-related heart diseases. Future research can reveal the independent and combined effects of different fat depots on cardiac metabolism. Identifying high-risk patients and developing targeted therapies can prevent various obesity-related cardiac diseases. Further studies are needed to determine if correcting cardiac metabolic disturbances through metabolic therapies can reduce the prevalence of heart failure in this population **(Figs. 2 and 3)**.



FIGS. 1A AND B: Cardiac metabolism in normal and obese conditions.
(ATP: adenosine triphosphate; FA: fatty acid)

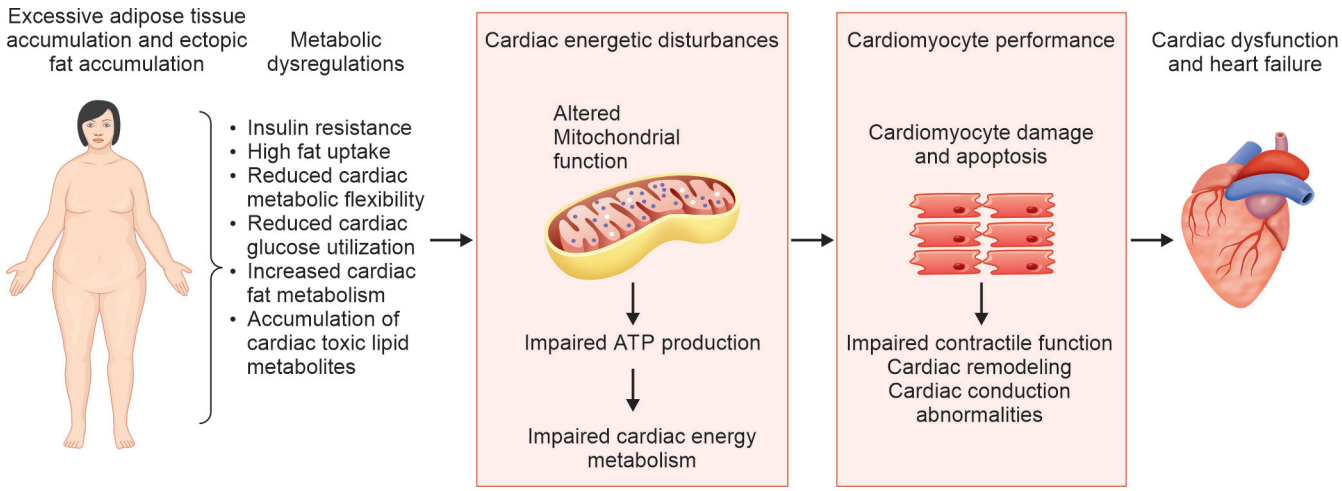


FIG. 2: Accumulation of ectopic fat and cardiac dysfunction: The pathophysiological link.

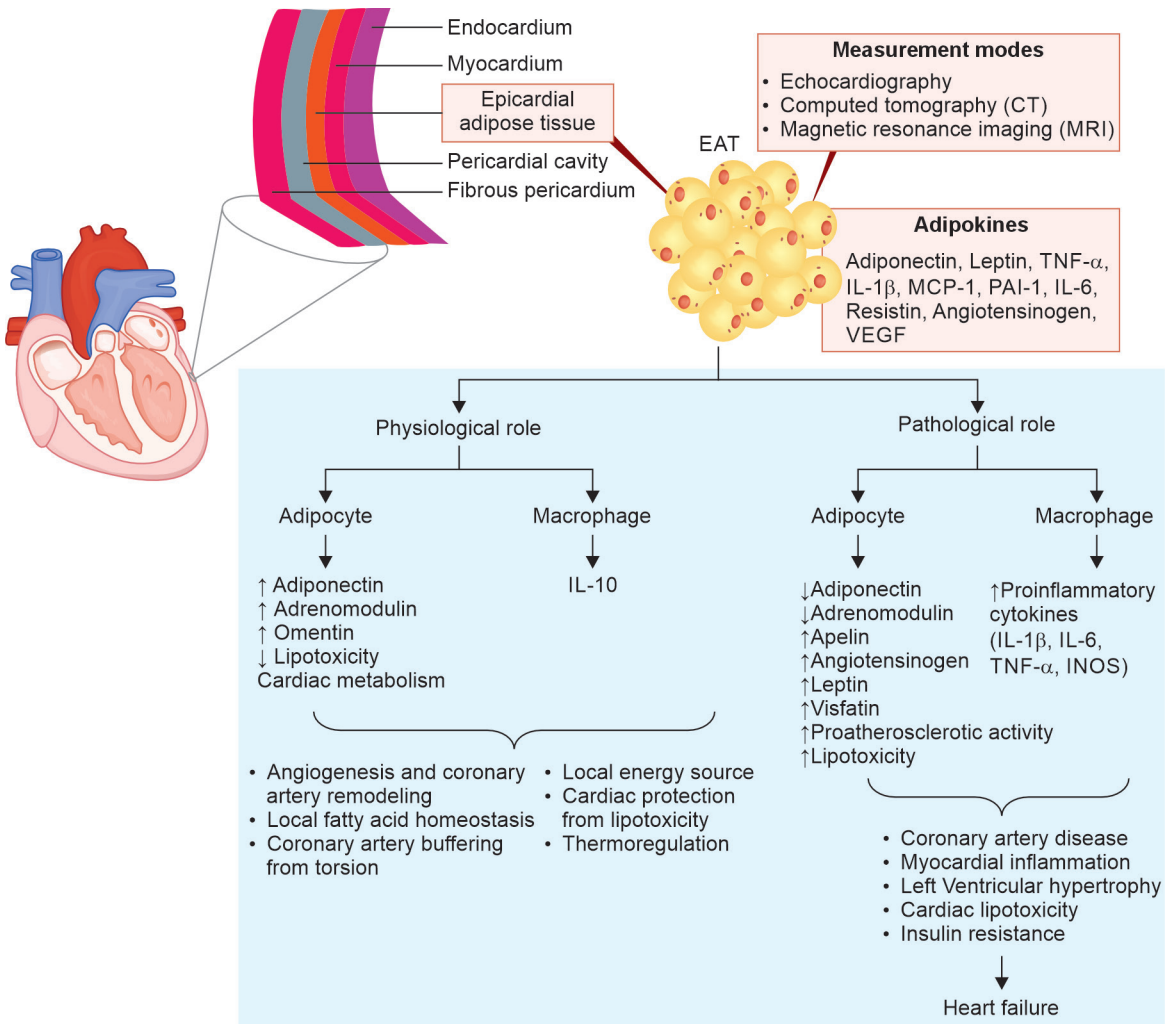


FIG. 3: Epicardial adipose tissue: Physiological and pathophysiological roles.

Epicardial adipose tissue (EAT) and perivascular adipose tissue (PVAT) differ in anatomical, embryological, and biochemical characteristics. EAT is closely connected to the myocardium, shares blood supply with coronary arteries, provides mechanical support, and serves as an energy depot for the myocardium. EAT provides up to 50–70% of the energy used for myocardium contraction, and its dysfunction is associated with impaired glucose and lipid uptake, causing conditions like obesity, diabetes, and heart failure. EAT accumulation can lead to myocardial steatosis and lipotoxic cardiomyopathy. It also exhibits a specific secretome pattern with proinflammatory mediators, causing atherosclerosis and inflammation. PVAT surrounding arteries has an anti-inflammatory role but can become proinflammatory in obesity. PVAT expansion is linked to adverse vascular function, neointimal formation, and hypertension. While further research is needed, EAT and PVAT have potential as markers of cardiometabolic risk and therapeutic targets.

ECTOPIC FAT IN THE HEPATIC HEALTH

Excess lipid accumulation in hepatocytes causes various histological alterations, ranging from steatosis to nonalcoholic steatohepatitis (NASH) and eventually cirrhosis. NASH-related cirrhosis can also result in hepatocellular carcinoma, with mortality rates similar to or worse than those of hepatitis C-related cirrhosis. NAFLD is characterized by the presence of fat (TGs) in >5% of hepatocytes. An imbalance in TG storage and release triggers NAFLD, leading to inflammation, steatonecrosis, and fibrosis. Insulin resistance is associated with lipid accumulation in nonadipose tissues like muscle and the liver. The relationship between NAFLD and insulin resistance remains complex, with unclear causality. Peripheral insulin resistance affects glucose uptake in skeletal muscle, while in adipose tissue, insulin resistance impairs antilipolytic action and increases fatty acid release. Elevated glucose and fatty acid levels promote hepatic fatty acid and TG uptake and synthesis, leading to hepatic steatosis. In addition to peripheral insulin resistance, intrahepatic alterations in glucose and fat metabolism can independently cause steatosis. Short-term high-fat diet feeding can result in hepatic fat accumulation and insulin resistance, even without peripheral fat accumulation. Advanced liver disease reduces insulin clearance and contributes to hyperinsulinemia. Liver fat content correlates with impaired insulin clearance and hepatic insulin sensitivity. NAFLD symptoms vary, with some individuals having no noticeable symptoms, while others may present with hyperglycemia and classic diabetes symptoms. Also, fatty liver disease is an independent predictor of a higher heart rate and early cardiac remodeling associated with reduced ventricular volumes. South Asian men and women appear to store more ectopic fat in the liver compared with their white European counterparts with similar body mass index (BMI) levels. Given the emerging understanding of the importance of liver fat in diabetes pathogenesis, these findings help explain the greater diabetes risks in South Asians **(Figs. 4 and 5)**.

Multiple factors contribute to NAFLD, including oxidative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, hypoxia, adipocytokine imbalance, hypothalamic signaling alterations, and changes in the gut microbiota. Lifestyle interventions focusing on weight loss are the first-line treatment for NAFLD, with bariatric surgery showing significant benefits. Vitamin E is recommended for nondiabetic patients, while glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are beneficial for diabetic patients. Statins may reduce cardiovascular risk in dyslipidemia patients with NAFLD or NASH. Also, several antifibrotic agents [like peroxisome proliferator-activated receptor (PPAR) agonists, Farnesoid X receptor (FXR) agonists, apoptosis signal-regulating kinase 1 (ASK-1) inhibitors, chemokine receptor 2 (CCR2)/CCR5 chemokine receptor blockers, galectin antagonists, and siRNA targets downregulating heat shock protein] are being tested.

Ectopic Fat in Skeletal Muscle

Skeletal muscle adiposity includes perimuscular, intermuscular (INTMF), intramuscular (IM), para-osseal fat, and intramyocellular lipid accumulation (IMCL). INTMF and IMCL are more identifiable and correlate with genetic, environmental, and metabolic factors. INTMF increases with age and BMI and is more common in African-Americans. In obese individuals, IMCL increases with lipid overflow, causing incomplete β-oxidation,

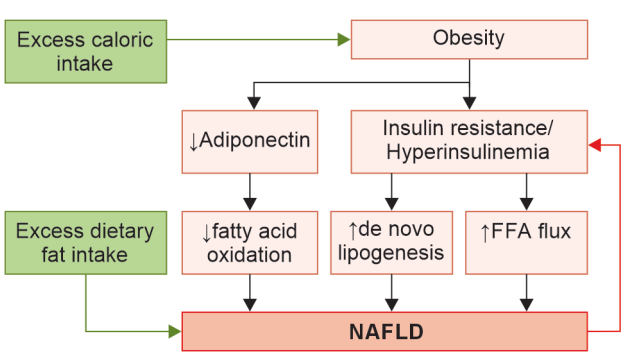


FIG. 4: Excess calorie intake, insulin resistance, and NAFLD: The vicious cycle.
(FFA: free fatty acid; NAFLD: nonalcoholic fatty liver disease)

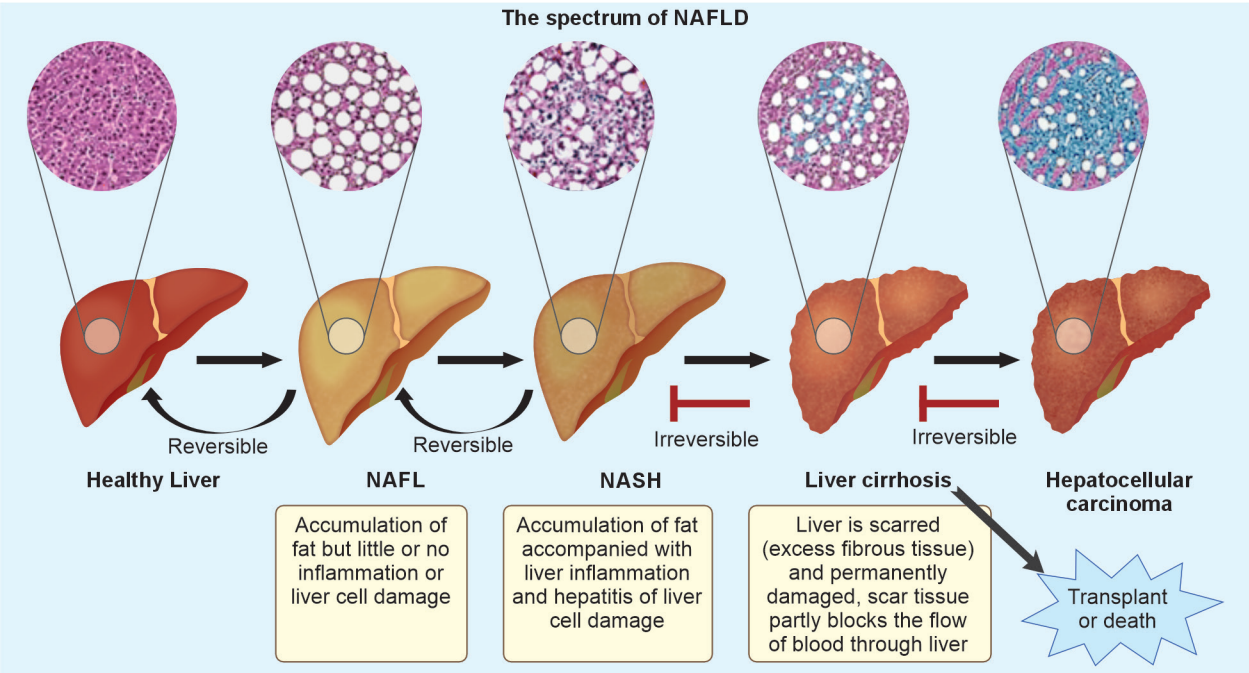


FIG. 5: NAFLD progression: Spectrum of pathological changes.
(NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis)

reactive oxygen species (ROS) formation, and insulin resistance, while trained athletes with comparable IMCL levels are insulin sensitive, known as "the athlete's paradox". INTMF and IMCL correlate with fasting glucose and insulin resistance independent of subcutaneous fat tissue. Skeletal muscle fat may have a direct clinical impact on the cardiometabolic risk. A preliminary artificial intelligence (AI)-based profiling of body composition from routine abdominal CT scans identified myosteatosis as a key predictor of mortality risk in asymptomatic adults.

Ectopic Fat in Renal Metabolism

Renal lipid accumulation plays an important role in the development and progression of CKD. Obese mice show lipid accumulation in glomerular and tubulointerstitial cells, causing a characteristic proteome signature with upregulated sterol regulatory element-binding protein and related genes. Renal insulin resistance also causes lipotoxicity, as observed in diabetic mice where specific insulin receptor deletion causes glomerulosclerosis. Podocytes are vulnerable to nonesterified fatty acid (NEFA) accumulation, while mesangial cells' scavenging function is reduced by lipid overload, causing lipid accumulation, apoptosis, and foam cell formation. In tubular cells, TG accumulation disrupts mitochondrial function, triggering autophagy, renal gluconeogenesis, tubulointerstitial fibrosis, and lipoapoptosis. These mechanisms cause obesity-related glomerulopathy, a form of focal segmental glomerulosclerosis with early glomerular hyperfiltration, mesangial proliferation, and lipid deposition in mesangial and tubular cells. Therapeutic approaches targeting lipid overload hold promise in preventing kidney injury.

Ectopic Fat in Pancreas Health

Pancreas volume decreases with age, while pancreatic adipose content increases. Nonalcoholic fatty pancreatic steatosis (NAFPD) prevalence varies (higher rates in males and obese individuals). NAFPD is mainly due to pancreatic fatty infiltration, leading to nonalcoholic steatopancreatitis (NASP) which may contribute to atherosclerosis and β-cell dysfunction. Unsaturated fatty acids released from peripancreatic fat might worsen acute pancreatitis. Weight loss through a Mediterranean diet and physical activity reduces pancreatic fat, but its effect is lower than on other fat deposits. Bariatric surgery and certain drugs show promising effects in reducing pancreatic fat and improving glycemic control.

Ectopic Fat and Diabetes

Ectopic fat may cause organ-specific insulin resistance, termed "lipotoxicity." Some individuals with type 2 diabetes mellitus (T2DM) predisposition accumulate more visceral fat due to impaired subcutaneous fat

storage. Lipodystrophy exemplifies this concept, with fat accumulation in visceral and ectopic tissues causing insulin resistance. On the other hand, some individuals, particularly women with high BMIs, remain insulin-sensitive due to low levels of visceral and ectopic fat but high subcutaneous fat content. PPAR-γ agonists illustrate the impact of ectopic fat on dysglycemia by redistributing fat away from the liver and increasing subcutaneous fat. Transplanting adipose tissue into lipoatrophic mice normalizes hepatic insulin sensitivity by removing excess hepatic fat **(Fig. 6)**.

MINERALOCORTICOID RECEPTORS' ROLE IN ECTOPIC FAT ACCUMULATION

Mineralocorticoid, a nuclear receptor, binds to aldosterone and cortisol, acting as a transcription factor. It regulates volume status, blood pressure, and electrolyte balance in various tissues, including the kidney. MR has been discovered in nonepithelial tissues, thereby extending MR's role beyond electrolyte homeostasis. MR activity is linked to pro-inflammatory, pro-oxidative, and pro-fibrotic changes in target tissues, causing cardiometabolic diseases. MR is expressed in brown adipose tissue (BAT) and white adipose tissue (WAT) and has a key role in preadipocyte differentiation, driving the acquisition of a mature phenotype. The exposure of cultured 3T3-L1 cells to aldosterone increased intracellular lipid content and expression of adipocyte conversion markers like adiponectin and leptin, causing an increased white adipocyte phenotype. In obesity, MR is overexpressed in adipose tissue, suggesting its involvement in adipocyte dysfunction and metabolic complications. The mechanisms underlying MR overactivity in obesity remain unclear **(Fig. 7)**.

HEPATOKINES AND ECTOPIC FAT

ssAdvancements in genetics, transcriptomics, and proteomics have revealed the liver's central role in metabolism. Hepatocytes release hepatokines, which are hormone-like proteins. In NAFLD, the hepatokine secretory profile is disturbed, and NAFLD often precedes dysfunction in other organs during the pathogenesis of

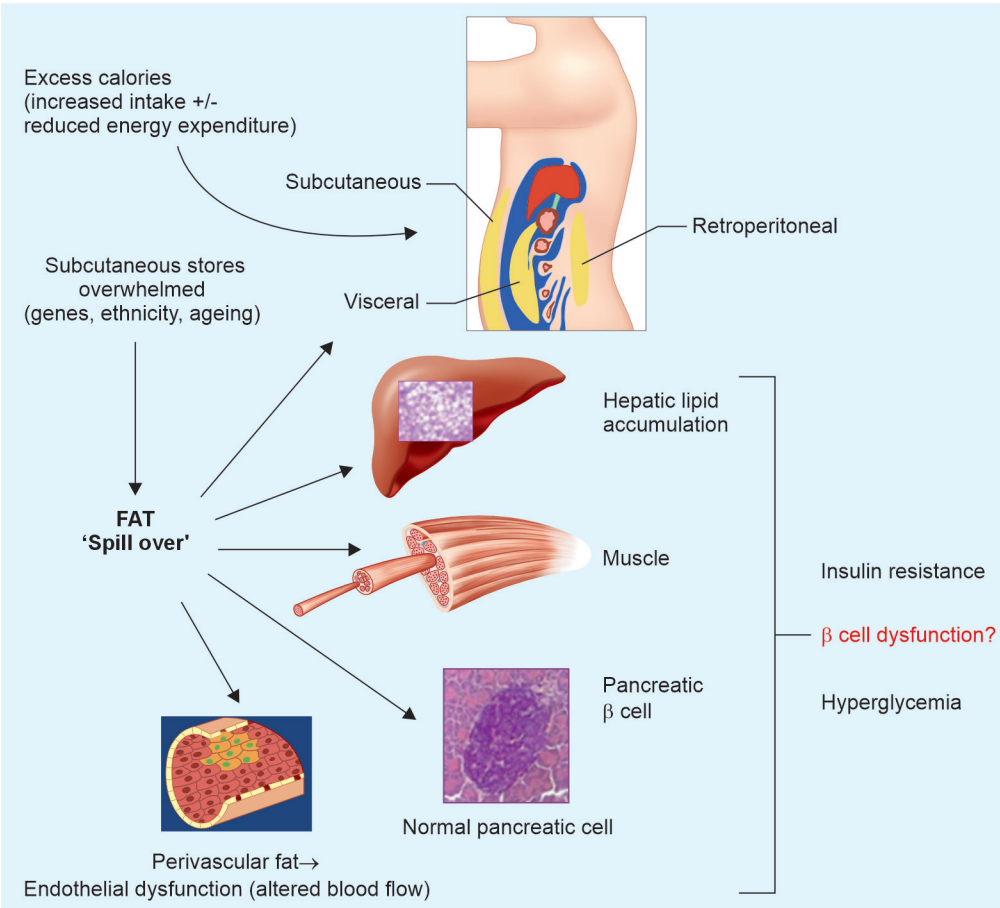


FIG. 6: Ectopic fat distribution and insulin resistance.

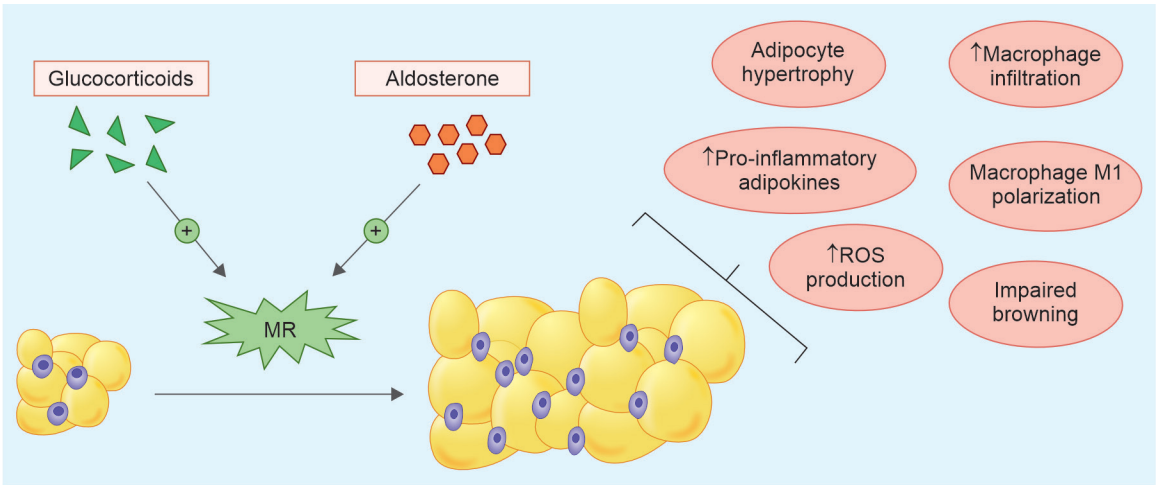


FIG. 7: Mineralocorticoid (MR) signaling and adipocytes hypertrophy.
(ROS: reactive oxygen species)

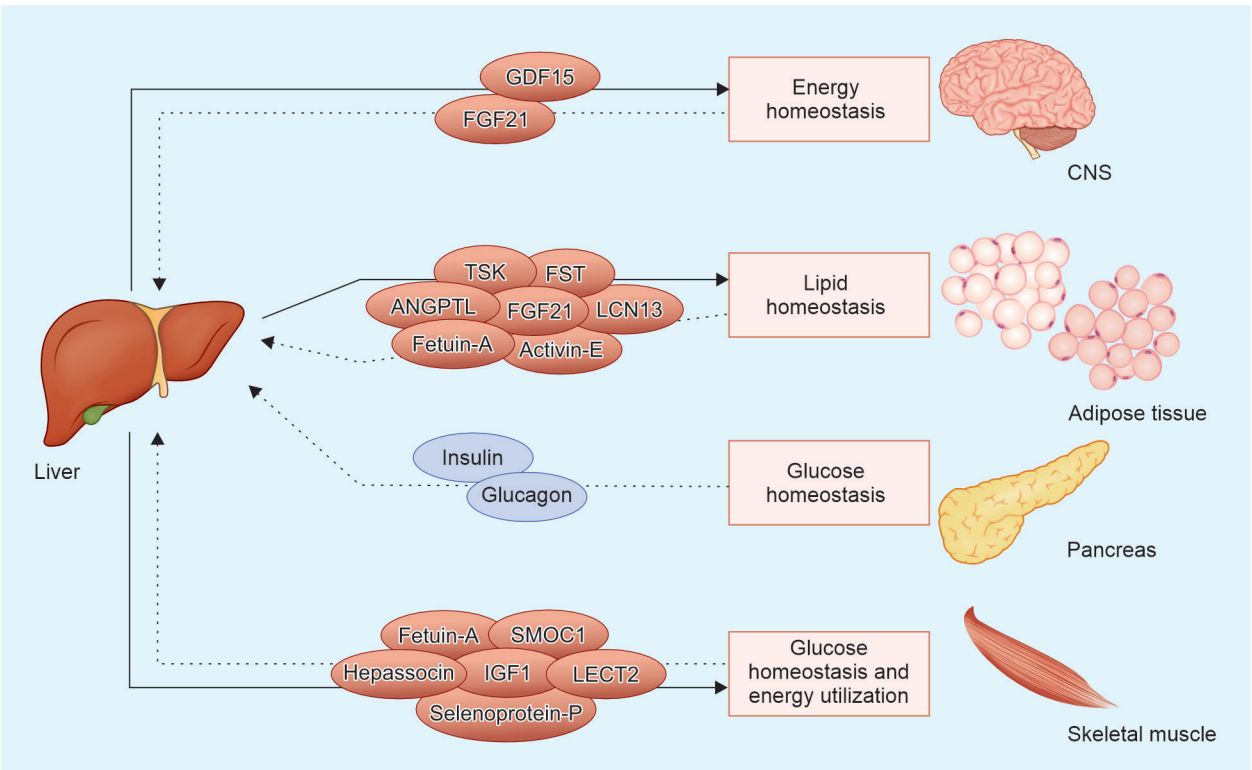


FIG. 8: Hepatokines and their roles.

systemic metabolic diseases. This altered hepatokines' secretion disrupts interorgan signaling, leading to complex metabolic dysregulation. More than 20 hepatokines have been identified and studied to establish their hepatic expression in the fatty liver and their metabolic effects **(Figs. 8 and 9)**.

ECTOPIC FAT: MANAGEMENT

Key approaches for managing ectopic fat are as follows:

- *Lifestyle modifications:*
  - A balanced diet and regular exercise are the foundation of ectopic fat management.
  - Aim to promote a healthy body weight and reduce ectopic fat deposition.

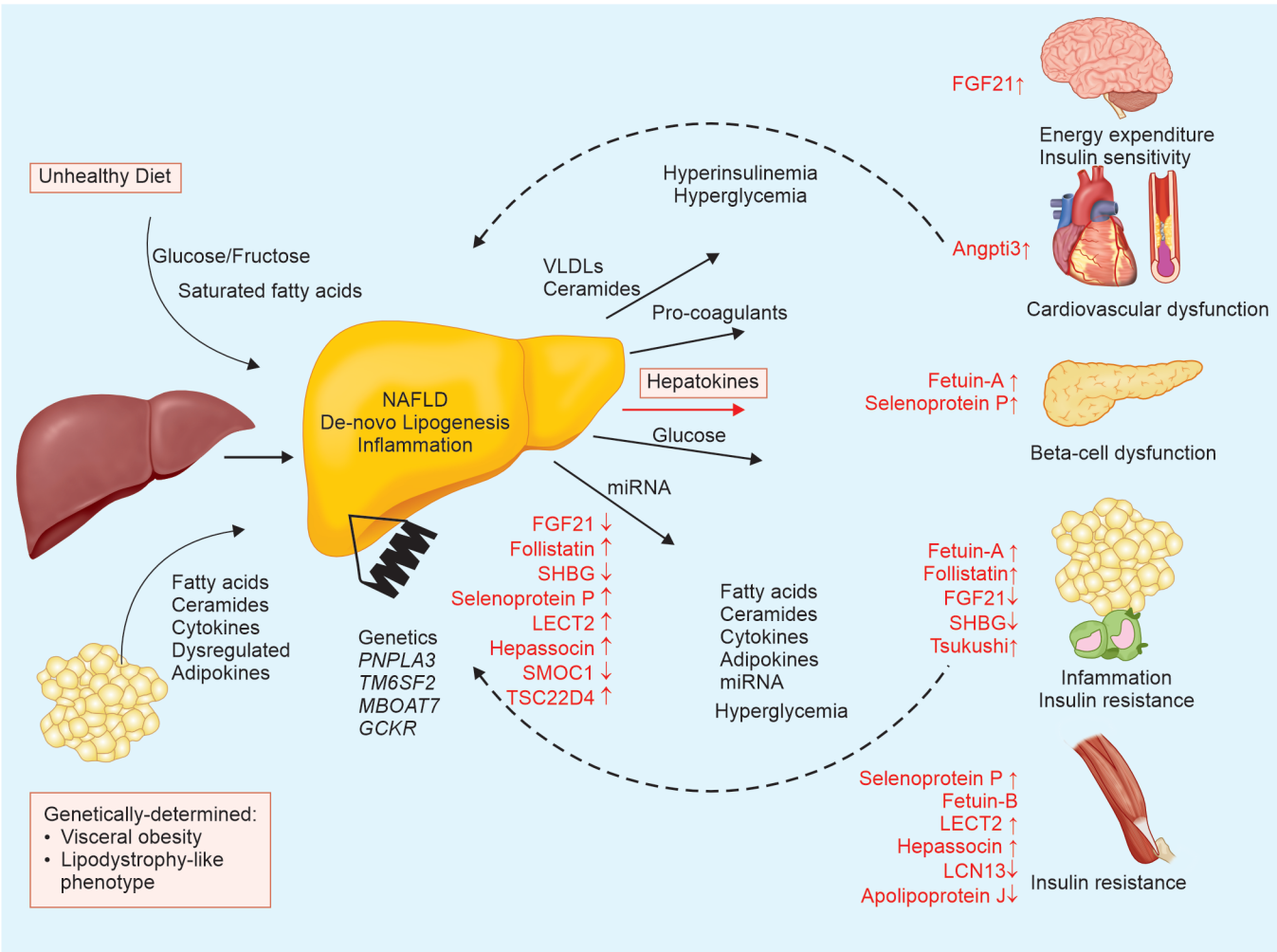


FIG. 9: NAFLD, hepatokines, and metabolic complications: Pathophysiological link.
(NAFLD: nonalcoholic fatty liver disease)

- *Pharmacological interventions:* These may be considered in certain cases, especially when lifestyle modifications alone are insufficient.
  - *Insulin sensitizers*: Metformin
  - MR antagonists: Spironolactone and eplerenone
  - Lipid-lowering agents: Statins
  - Incretin mimetics: Liraglutide
  - SGLT-2 inhibitors are also being studied.
  - Saroglitazar, vitamin E, and PPAR-γ agonists have shown promising results in NAFLD.
- *Surgical interventions:*
  - Bariatric surgery
  - Can also be considered in severe cases of ectopic fat deposition in critical organs

CONCLUSION

With increased life expectancy, there is an increase in chronic diseases and negative quality of life. Ectopic fat accumulation has now emerged as the main player in various disease conditions. With improvements in diagnostic capabilities and more focused research to mitigate ectopic fat, various disease conditions can be prevented, managed, and even cured. More research targeting adipocyte conversion, angiogenesis, and epigenetic modulations can pave the way to halt the "ectopic endemic". While the roles of mineralocorticoid receptors and hepatokines are promising, further research is needed to identify them as potential targets for the management of ectopic fat.

SUGGESTED READINGS

1. Snel M, Jonker JT, Schoones J, Lamb H, de Roos A, Pijl H, et al. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol. 2012;2012:983814.
2. Lettner A, Roden M. Ectopic fat and insulin resistance. Curr Diab Rep. 2008;8:185-91.
3. Piché M-E, Poirier P. Obesity, ectopic fat and cardiac metabolism. Expert Rev Endocrinol Metab. 2018;13(4):213-21.
4. Lu Z, Jiang Z, Tang J, Lin C-P, Zhang H. Functions and origins of cardiac fat. FEBS J. 2023;290(7):1705-18.
5. Aeddula NR, Cheungpasitporn W, Thongprayoon C, Pathireddy S. Epicardial adipose tissue and renal disease. J Clin Med. 2019;8(3):299.
6. Ferrara D, Montecucco F, Dallegri F, Carbone F. Impact of different ectopic fat depots on cardiovascular and metabolic diseases. J Cell Physiol. 2019;234(12):21630-41.
7. Liu Q, Bengmark S, Qu S. The role of hepatic fat accumulation in pathogenesis of non-alcoholic fatty liver disease (NAFLD). Lipids Health Dis. 2010;9:42.
8. Jamialahmadi O, Tavaglione F, Rawshani A, Ljungman C, Romeo S. Fatty liver disease, heart rate and cardiac remodelling: Evidence from the UK Biobank. Liver Int. 2023;43(6):1247-55.
9. Wang J, He W, Tsai P-J, Chen P-H, Ye M, Guo J, et al. Mutual interaction between endoplasmic reticulum and mitochondria in nonalcoholic fatty liver disease. Lipids Health Dis. 2020;19(1):72.
10. Nachit M, Horsmans Y, Summers RM, Leclercq IA, Pickhardt PJ. AI-based CT Body Composition Identifies Myosteatosis as Key Mortality Predictor in Asymptomatic Adults. Radiology. 2023;307(5):e222008.
11. Sattar N, Gill JMR. Type 2 diabetes as a disease of ectopic fat? BMC Med. 2014;12:123.
12. Parasiliti-Caprino M, Bollati M, Merlo FD, Ghigo E, Maccario M, Bo S. Adipose tissue dysfunction in obesity: Role of mineralocorticoid receptor. Nutrients. 2022;14(22):4735.
13. Infante M, Armani A, Marzolla V, Fabbri A, Caprio M. Adipocyte mineralocorticoid receptor. In: Litwack G (Ed). Vitamins and Hormones, 109th edition. Philadelphia: Elsevier B.V.; 2019. pp. 189-209.
14. Kim TH, Hong D-G, Yang YM. Hepatokines and non-alcoholic fatty liver disease: Linking liver pathophysiology to metabolism. Biomedicines. 2021;9(12):1903.
15. Stefan N, Schick F, Birkenfeld AL, Häring H-U, White MF. The role of hepatokines in NAFLD. Cell Metab. 2023;35(2):236-52.
16. Jensen-Cody SO, Potthoff MJ. Hepatokines and metabolism: Deciphering communication from the liver. Mol Metab. 2021;44:101138.
17. Hens W, Taeyman J, Cornelis J, Gielen J, Gaal L Van, Vissers D. The Effect of Lifestyle Interventions on Excess Ectopic Fat Deposition Measured by Noninvasive Techniques in Overweight and Obese Adults: A Systematic Review and Meta-Analysis. J Phys Act Heal. 2016;13(6):671-94.
18. Wang C, Liu F, Yuan Y, Wu J, Wang H, Zhang L, et al. Metformin suppresses lipid accumulation in skeletal muscle by promoting fatty acid oxidation. Clin Lab. 2014;60(6):887-96.
19. Hulse JL, Habibi J, Igbekele AE, Zhang B, Li J, Whaley-Connell A, et al. Mineralocorticoid Receptors Mediate Diet-Induced Lipid Infiltration of Skeletal Muscle and Insulin Resistance. Endocrinology. 2022;163(11):bqac145.
20. Zhou M, Wang H, Chen J, Zhao L. Epicardial adipose tissue and atrial fibrillation: Possible mechanisms, potential therapies, and future directions. Pacing Clin Electrophysiol. 2020;43(1):133-45.
21. He F, Chen W, Xu W, Liu D, Xiao Z, Tang Y, et al. Safety and efficacy of liraglutide on reducing visceral and ectopic fat in adults with or without type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2023;25(3):664-74.
22. Angelini G, Gissey LC, Corpo G Del, Giordano C, Cerbelli B, Severino A, et al. New insight into the mechanisms of ectopic fat deposition improvement after bariatric surgery. Sci Rep. 2019;9(1):17315.