EKTOPİK YAĞLANMANIN DİYABETİK ORGAN DİSFONKSİYONLARINDAKİ ROLÜ

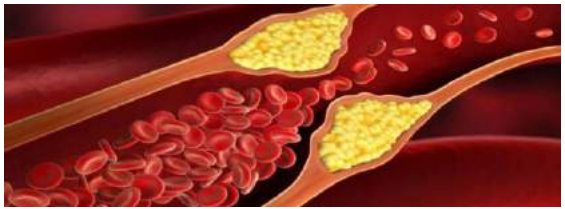
PERİVASKÜLER / EPİKARDİYAL / HEMATOPOETİK SİSTEMDE YAĞLANMA

Prof. Dr. Engin GÜNEY
Aydın Adnan Menderes Üniversitesi Tıp Fakültesi
Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı

57. ULUSAL DİYABET KONGRESİ

Sigara

Hiperlipidemi



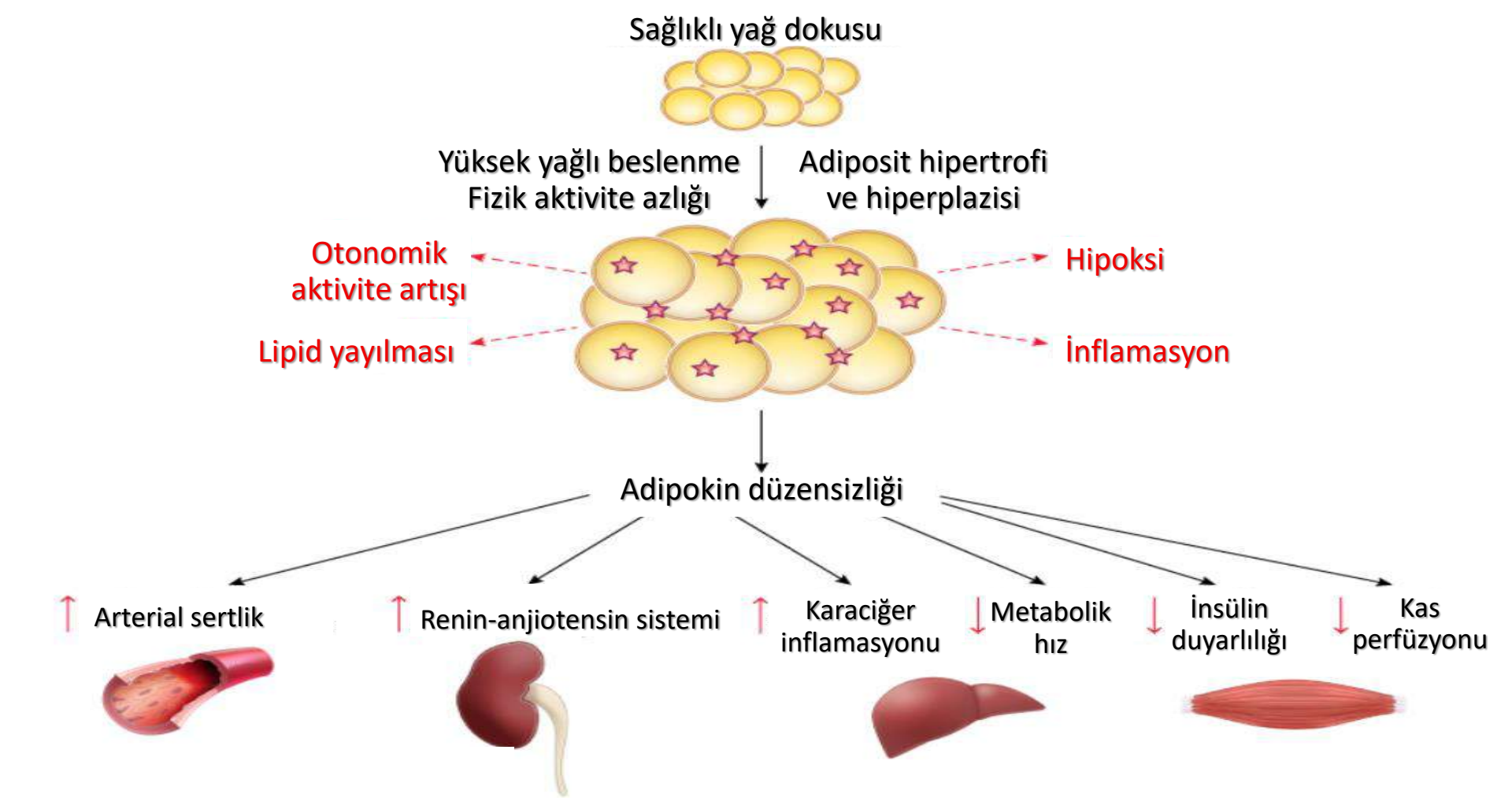
Hipertansiyon

Obezite
Tip 2 Diyabet

Kardiyovasküler hastalık

Mortalite

- Ford ES et al. N Engl J Med 2007;356:2388-98.
- Artinian NT et al. Circulation 2010;122:406-41.

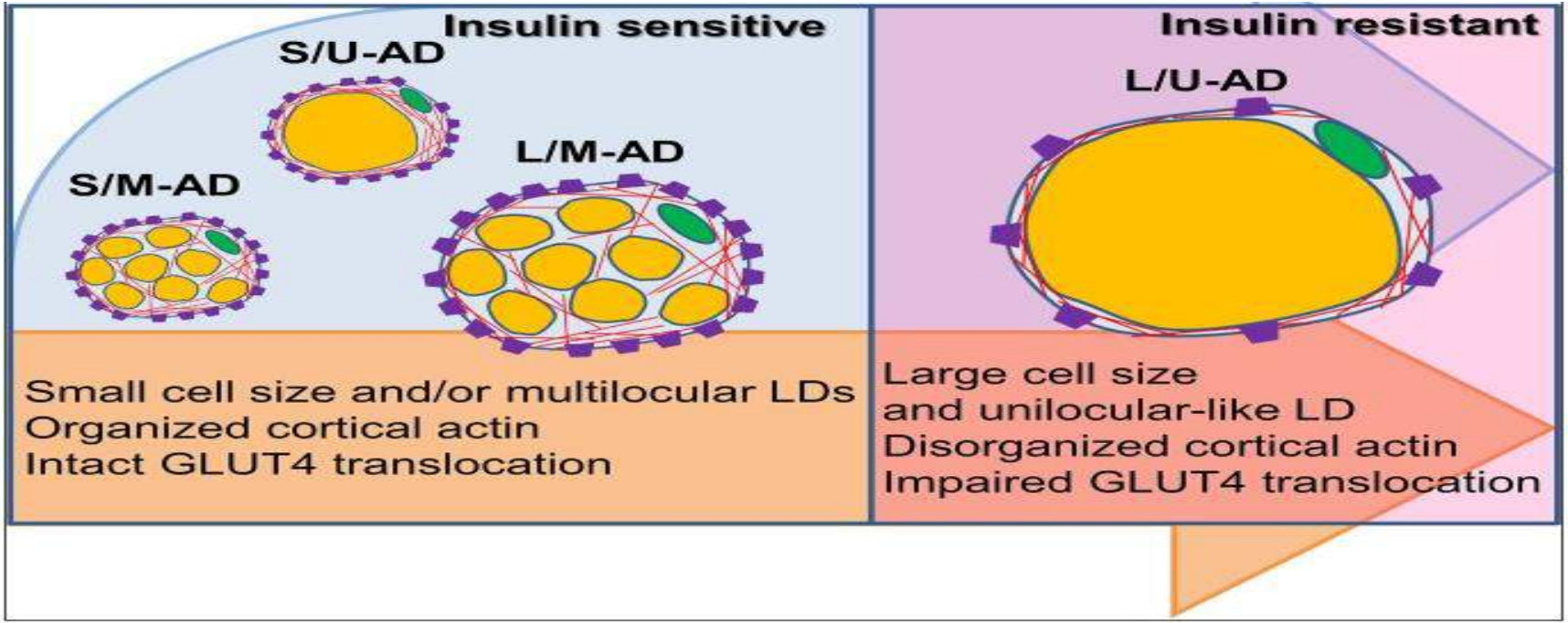


❖ Saxton SN et al. Physiol Rev 2019;99:1701-63.

AMERICAN SOCIETY FOR MICROBIOLOGY | Molecular and Cellular Biology®

Lipid-Overloaded Enlarged Adipocytes Provoke Insulin Resistance Independent of Inflammation

Jong In Kim,[a] Jin Young Huh,[a] Jee Hyung Sohn,[a] Sung Sik Choe,[a] Yun Sok Lee,[b,e] Chun Yan Lim,[c] Ala Jo,[d] Seung Bum Park,[d] Weiping Han,[c] Jae Bum Kim[a]



❖ Kim JI et al. Mol Cell Biol 2015;35:1686-99.

0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(6):2548–2556

doi: 10.1210/jc.2004-0395

Adipose Tissue as an Endocrine Organ

ERIN E. KERSHAW AND JEFFREY S. FLIER

TABLE 1. Examples of adipocyte-derived proteins with endocrine functions

Cytokines and cytokine-related proteins	Leptin
	TNFα
	IL-6
Other immune-related proteins	MCP-1
	NEFAs
Enzymes involved in steroid metabolism	Cytochrome P450-dependent aromatase
	17βHSD
	11βHSD1
Proteins of the RAS	AGT
Other proteins	Resistin

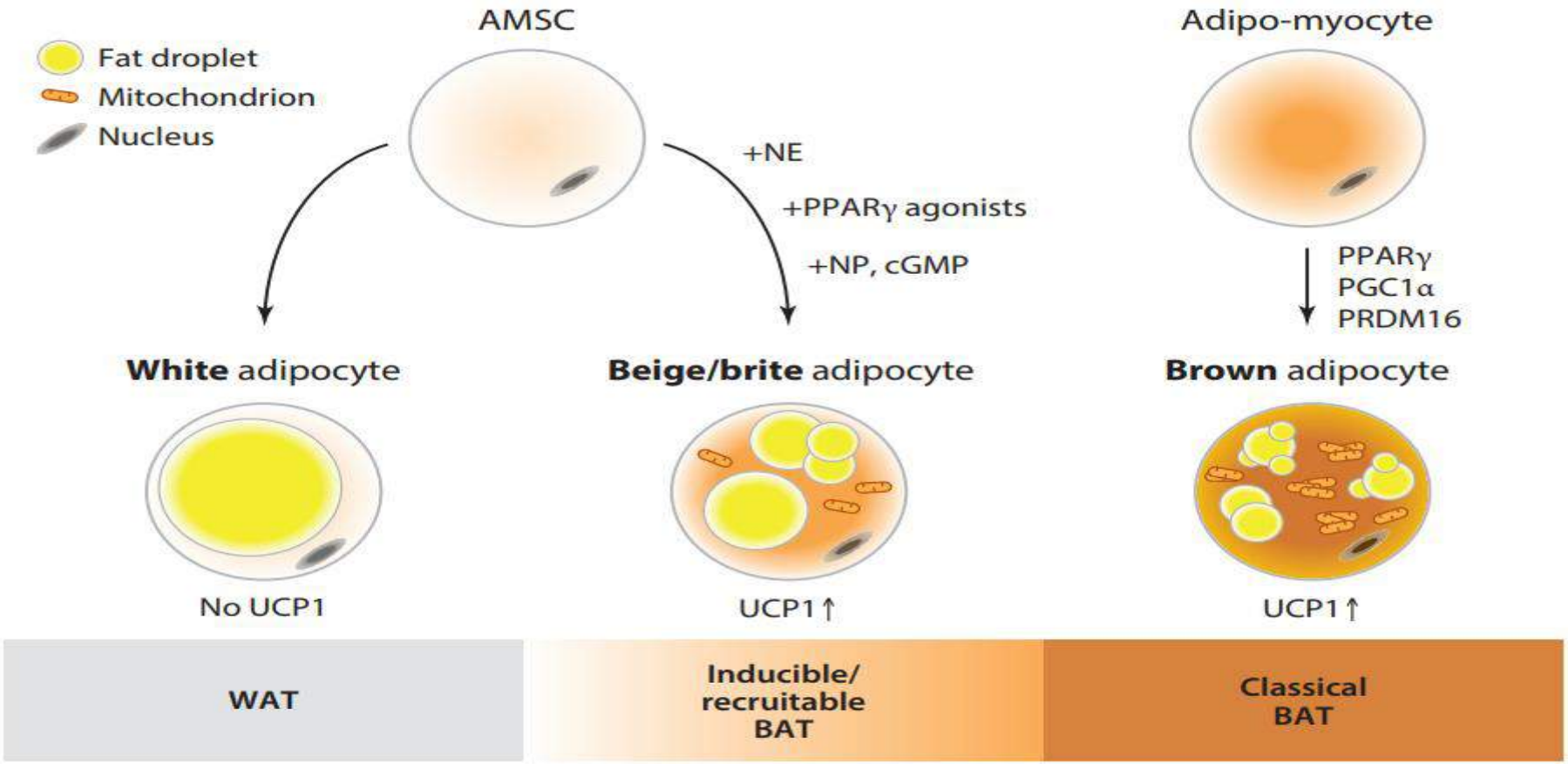
TABLE 2. Examples of receptors expressed in adipose tissue

Receptors for traditional endocrine hormones	Insulin receptor
	Glucagon receptor
	GH receptor
	TSH receptor
	Gastrin/CCK-B receptor
	Estrogen receptor
	Progesterone receptor
Cytokine receptors	Leptin receptor
	IL-6 receptor
	TNFα receptor
Catecholamine receptors	β1, β2, β3 receptors
	α1, α2 receptors

Proceedings of the Nutrition Society (2001), **60**, 329–339

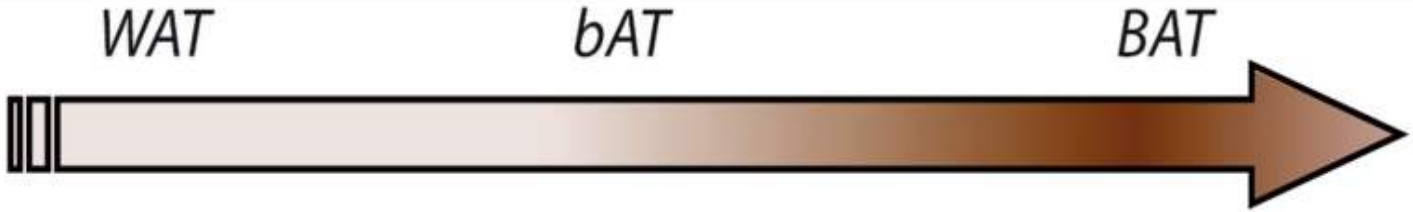
Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ

Paul Trayhurn[1]* and John H. Beattie[2]



❖ Pfeifer A, Hoffmann LS. Annu Rev Pharmacol Toxicol 2015;55:207-27.

Table 1 Differences and similarities between the various adipose tissue depots



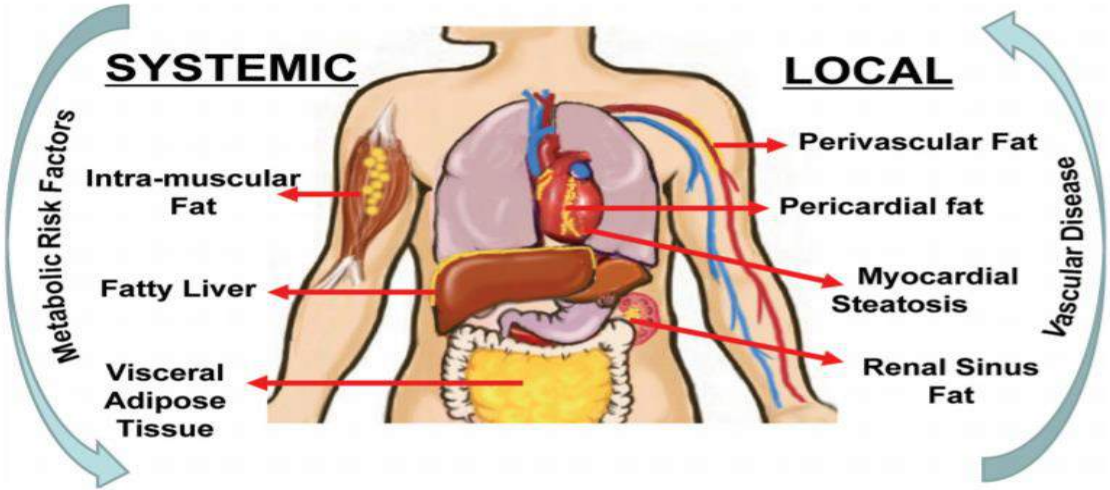
Body location	Gluteofemoral, subcutaneous and VAT	Inguinal and neck	Suprarenal, paravertebral and supraclavicular
Morphology	Big size and with a single LD	Intermediate size and with multiple LD	Variable size, vascularized and with multiple small LD
Mitochondria	+	++	+++
Function	Energy storage	Adaptive thermogenesis (UCP-1)	Non-shivering thermogenesis and energy dissipation
Obesogenity and diabetogenity	Positive	Negative	Negative

Body fat is stored as *WAT*, *bAT* or *BAT*. These depots can be distinguished by their location, size, mitochondria content, and function, playing diverse roles in obesity and T2D. Importantly, *WAT* could be browned to *bAT* and *BAT* by several approaches. *LD* stands for lipid droplet(s)

❖ Gonzalez N et al. Cardiovasc Diabetol 2017;16:44.

YAĞ DAĞILIMI

- Sistemik
  - Visseral yağ dokusu
  - Karaciğer ve kas yağ depoları
- Lokal
  - Perivasküler
  - Epikardiyal
  - Hematopoetik



❖ Britton KA, Fox CS. Circulation 2011;124:837-41.

PERİVASKÜLER YAĞ DOKUSU

	WAT	BAT	PVAT	References
Location	Subcutaneous and visceral	Suprarenal, interscapular, neck region in human infants	Surrounds blood vessels	Brown *et al.* (2014)
Morphology	Large adipocytes	Small adipocytes	Small adipocytes	Cedikova *et al.* (2016); Chatterjee *et al.* (2009)
Lipid droplet	Single, large	Multiple, small	Multiple, small	Brown *et al.* (2014); Cedikova *et al.* (2016); Chang *et al.* (2012)
Origin/development	Pdgfr-α progenitors	Myf5+ progenitors	SM22α + progenitors	Brown *et al.* (2014); Harms and Seale (2013)
Major function	Energy storage	Heat production	Vascular regulation, heat production	Chang *et al.* (2012); Harms and Seale (2013)
Mitochondria/UCP1	+/+ (nearly undetectable)	+++/+++	++(+)/++(+)	Cedikova *et al.* (2016)
Adipocyte-specific genes	PPAR-γ, PLIN1, HOXC8, TCF21, TLE3, C/EBPα, Rb, RIP140, APOL7C, DAPL1, NANT, SNCG, STAP1, GRAP2, MEST	ZIC1, LHX8, EVA1, PDK4, EPSTI1, PRDM16, CIDEA, ELOVL3, SCL27A2, COX7A1, CPT1B, KNG2m ACOT11, DIO2, BMP7	Similar to BAT	Cedikova *et al.* (2016); Fitzgibbons *et al.* (2011); Harms and Seale (2013)

❖ Nosalski R, Guzik TJ. Br J Pharmacol 2017;174:3486-513.

British Journal of Pharmacology

British Journal of Pharmacology (2017) **174** 3496–3513 3496

Themed Section: Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets?

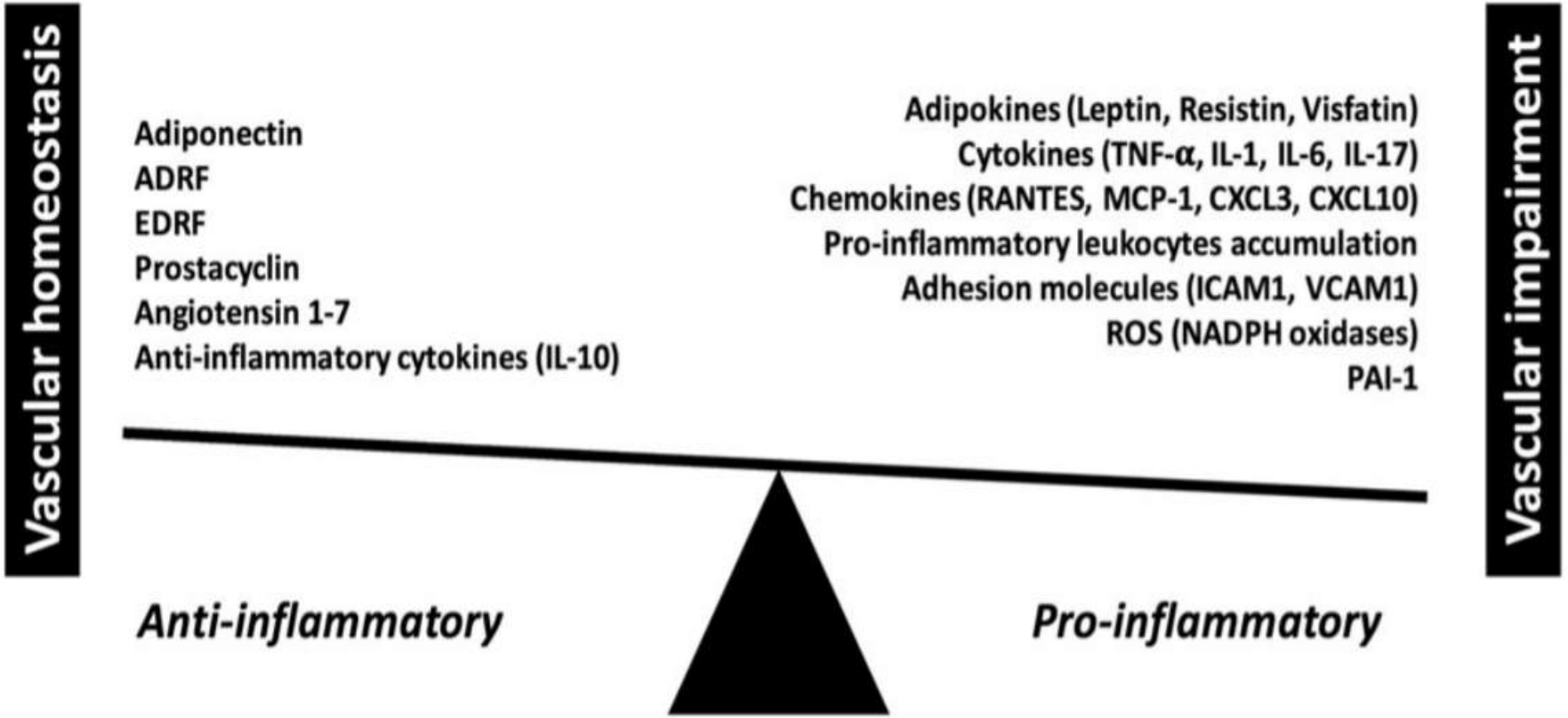
REVIEW ARTICLE

Perivascular adipose tissue inflammation in vascular disease

Ryszard Nosalski[1,2] and Tomasz J Guzik[1,2]

	PHYSIOLOGICAL STATE	HYPERTENSION	ATHEROSCLEROSIS
PVAT	Anti-inflammatory properties ↑Anti-inflammatory adipokines (adiponectin) ↑Accumulation of immune regulatory cells (T_{reg}) ↑Anti-inflammatory cytokines (IL-10) ↑ADRF (NO, H_2S, prostacyclin, Ang 1-7, etc.)	Pro-inflammatory properties ↑Pro-inflammatory adipokines (leptin, resistin, visfatin) ↓Anti-inflammatory adipokines (adiponectin) ↓Accumulation of regulatory cells ↑Immune cells accumulation (T cells, macrophages, DC, B cells, NK cells) ↑Pro-inflammatory cytokines ↑Chemokines ↑ROS ↑PVAT RAS activation	Pro-inflammatory properties ↑Pro-inflammatory adipokines (leptin, resistin, visfatin) ↓Anti-inflammatory adipokines (adiponectin) ↓Accumulation of regulatory cells ↑Immune cells accumulation (T cells, Macrophages, DC, B cells, NK cells) ↑Pro-inflammatory cytokines ↑Chemokines ↑ROS

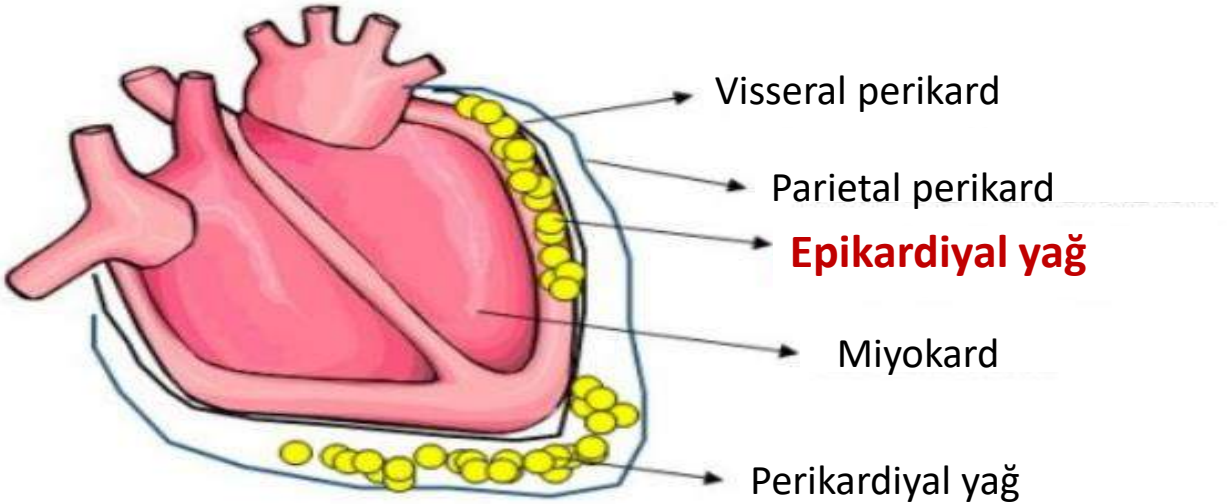
❖ Nosalski R, Guzik TJ. Br J Pharmacol 2017;174:3486-513.



❖ Nosalski R, Guzik TJ. Br J Pharmacol 2017;174:3486-513.

EPİKARDİYAL YAĞ DOKUSU

- Miyokard yüzeyi ve perikardın visseral tabakası arasındaki yağ dokusu



❖ Villasante Fricke AC et al. Int J Mol Sci 2019;20:5989.

EPİKARDİYAL YAĞ DOKUSU

- Fizyolojik koşullarda etkiler
  - Metabolik
    - Fazla SYA'nin emilimi
    - İskemi sırasında enerji sağlama
  - Termojenik
    - Aşırı ısıya karşı koruma
  - Mekanik
  - Yapısal
    - Adiponektin ve adrenomedullin sentezi

- Gruzdeva O et al. Lipids Health Dis 2018;17:218.

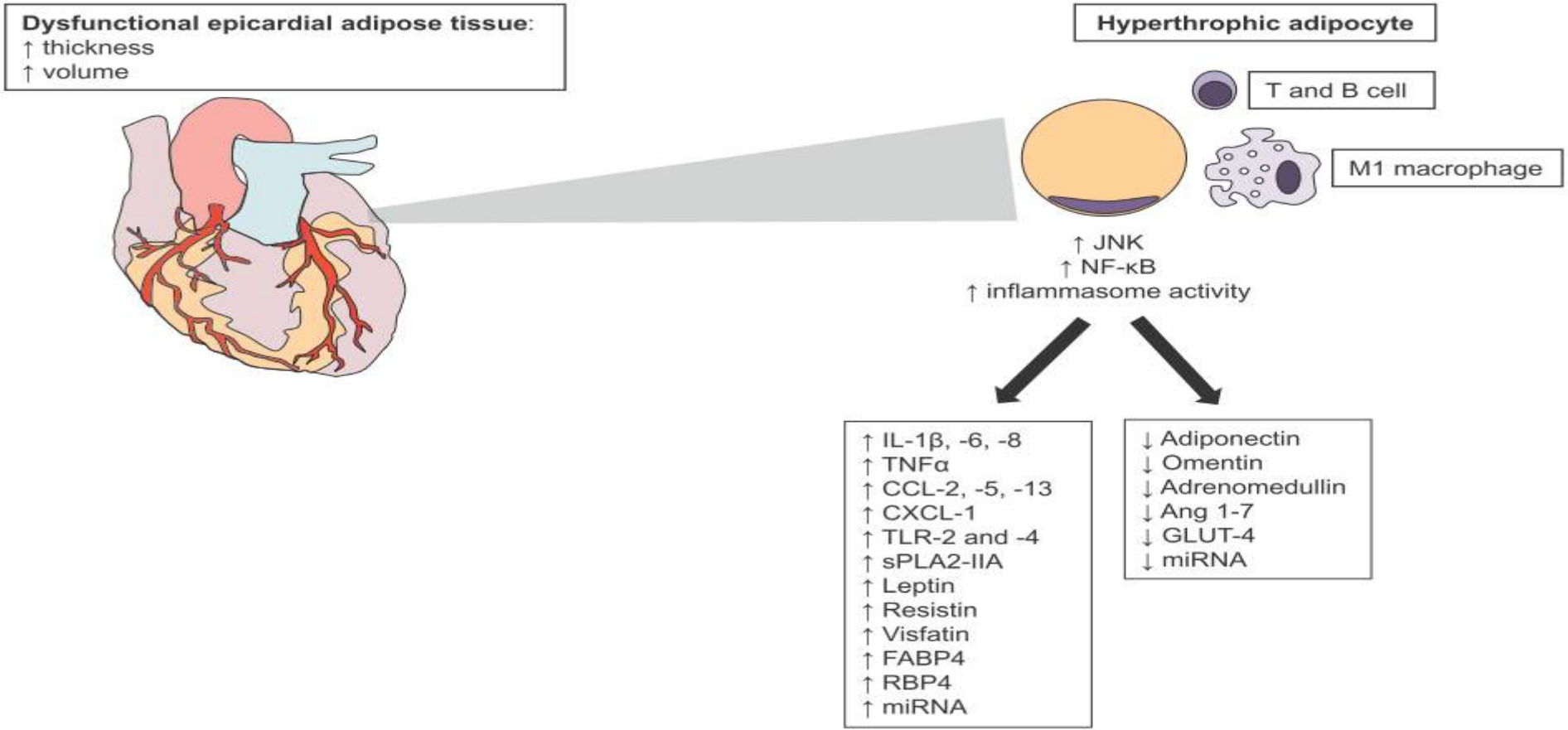
EPİKARDİYAL YAĞ DOKUSU

- Obezite koşullarında etkiler

  (artmış epikardiyal yağ dokusu)

- Miyokard hipertrofisi
- Kardiyomyositlerde fibroz ve apopitoz
- Adiponektin sentezinde azalma
- İnflamatuvar faktörlerin üretiminde artış

Gruzdeva O et al. Lipids Health Dis 2018;17:218.



❖ Ansaldo AM et al. Int J Cardiol 2019 PMID:30297191.

> Minerva Endocrinol. 2014 Jun;39(2):135-40.

Epicardial adipose tissue in patients with subclinical hypothyroidism

M Unubol [1], U Eryilmaz, E Guney, C Akgullu, I Kurt Omurlu

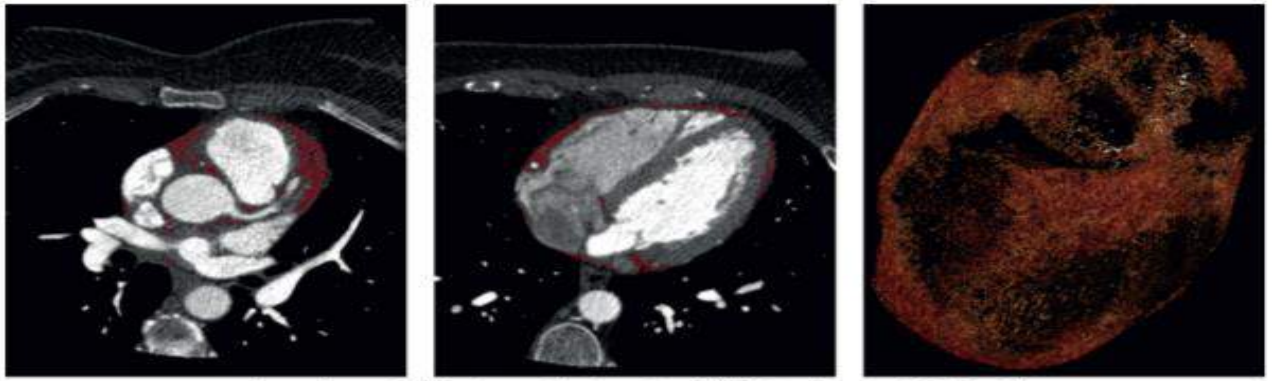
POLISH ARCHIVES OF INTERNAL MEDICINE 2019; 129 (11)

Diabetes enhances epicardial fat dysfunction

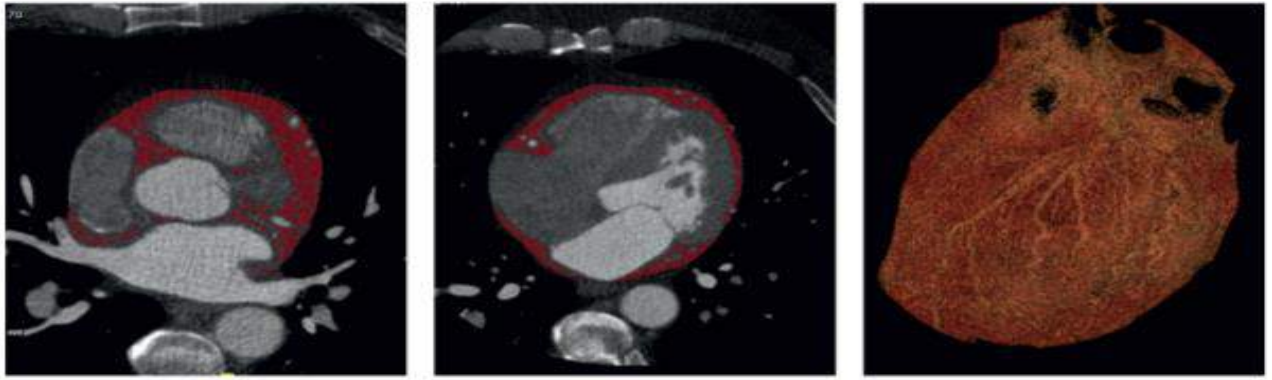
Ryszard Nosalski[1,2], Eman Oboud Alsheikh[2], Tomasz J. Guzik[1,2]

1 Department of Internal and Agricultural Medicine, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland
2 Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

FIGURE 2 Representative Examples of CT Epicardial Fat Volumes in a Lean and an Obese Patient With T2D



Lean Type 2 Diabetes patient, epicardial fat volume = 37.75cm^3



Obese Type 2 Diabetes patient, epicardial fat volume = 192.59cm^3

❖ Levelt E et al. J Am Coll Cardiol 2016;68:53-63.

HEMATOPOETİK YAĞ DOKUSU

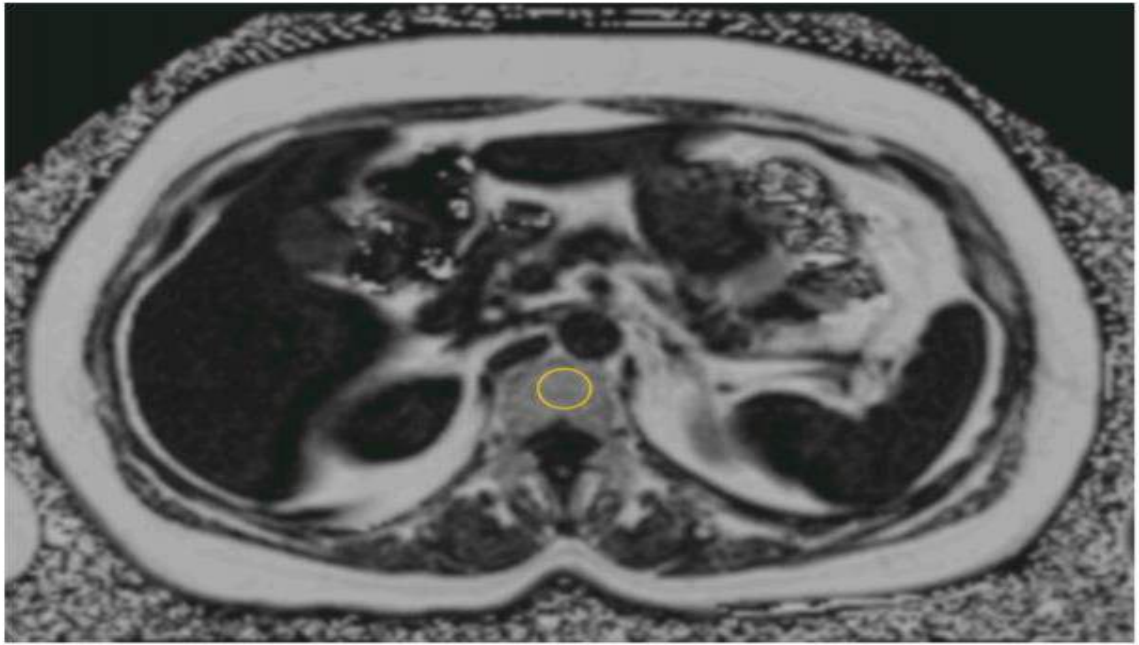


Figure 1. Assessment of bone marrow fat content in first lumbar vertebral body in the anterior part, medium level, avoiding vessels and the anterior border on a proton density fat fraction (PDFF) map with one region of interest with 2.0 cm^2 (ROI, yellow circle).

❖ Spurny M et al. Nutrients 2020;12:1509.

Bone. 2018 May ; 110: 134–140. doi:10.1016/j.bone.2018.01.008.

Development, regulation, metabolism and function of bone marrow adipose tissues

Ziru Li[1], **Julie Hardij**[1], **Devika P. Bagchi**[1], **Erica L. Scheller**[2], and **Ormond A. MacDougald**[1],

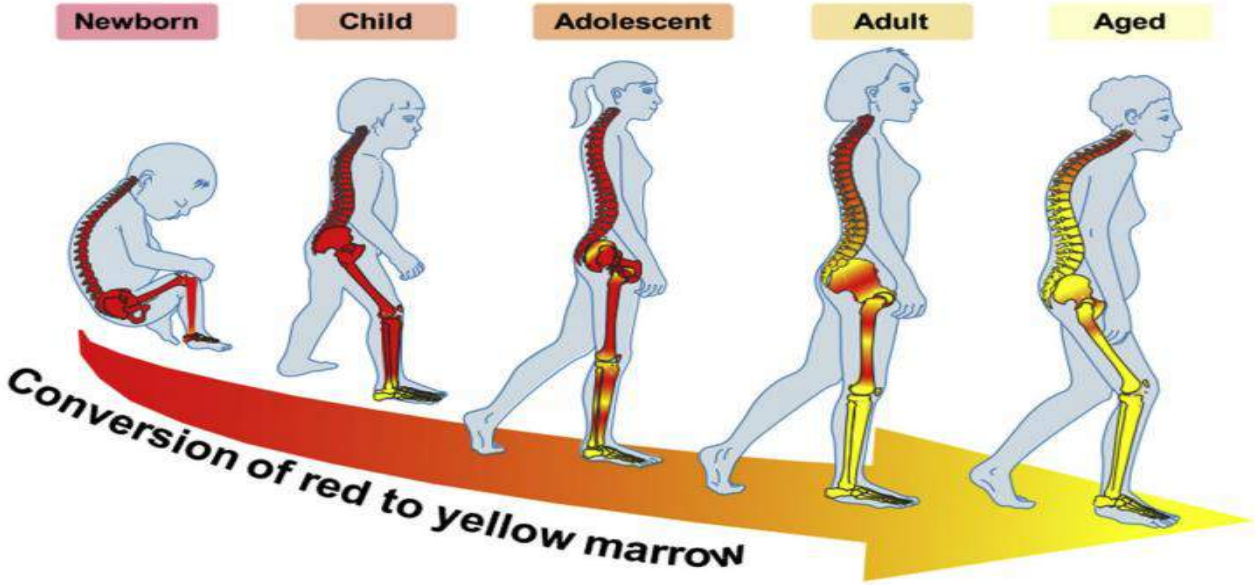


Figure 1. The conversion of red to yellow marrow during aging

Throughout life, hematopoietic cells are gradually replaced by adipocytes within bone marrow. This conversion of red to yellow marrow begins early in life and generally occurs in a centripetal pattern, beginning in the distal bones.

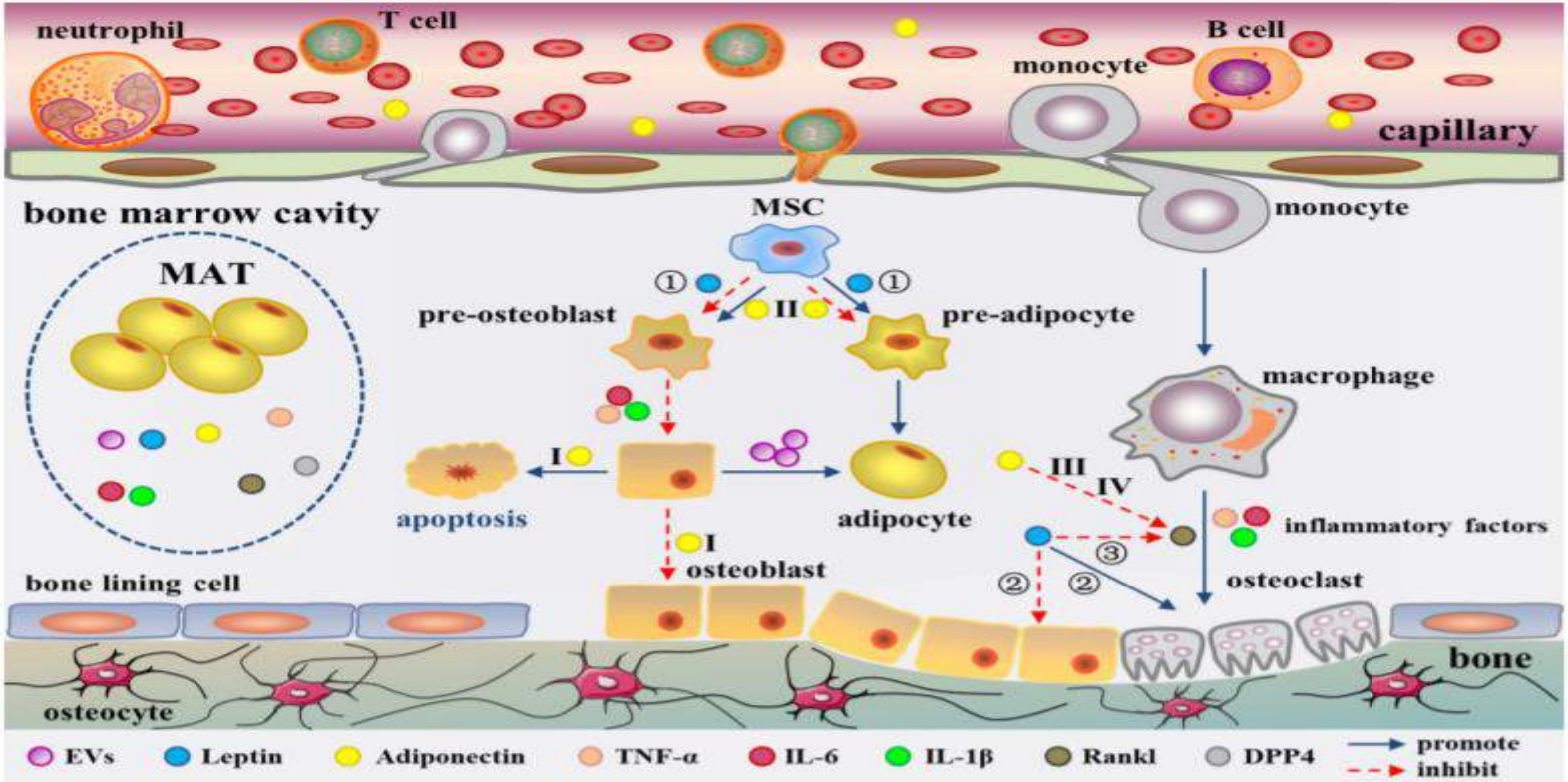


FIGURE 2 | Secretion of MAT as well as adipocyte-derived molecules in the regulation of bone metabolism in the bone marrow cavity. MAT could secrete EVs, leptin, adiponectin, inflammatory factors, RANKL, and DPP4. These factors regulate bone metabolism from different aspects. Among them, adiponectin has been confirmed to enter into the circulation. EVs cause a phenotypic transformation of osteoblast to adipocyte. Leptin regulates bone metabolism in three ways (①-③). Moreover, Adiponectin regulates bone metabolism through four pathways (I-IV). Inflammatory cytokines promote osteoclast formation and adipocyte differentiation. RANKL promote osteoclast formation. The role of DPP4 in bone marrow cavity remains unclear.

❖ Li Y et al. Front Endocrinol 2019;10:69.

Nutrition, Metabolism & Cardiovascular Diseases (2009) 19, 211—217

Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease

S. Eroglu*, L.E. Sade, A. Yildirir, U. Bal, S. Ozbicer, A.S. Ozgul, H. Bozbas, A. Aydinalp, H. Muderrisoglu

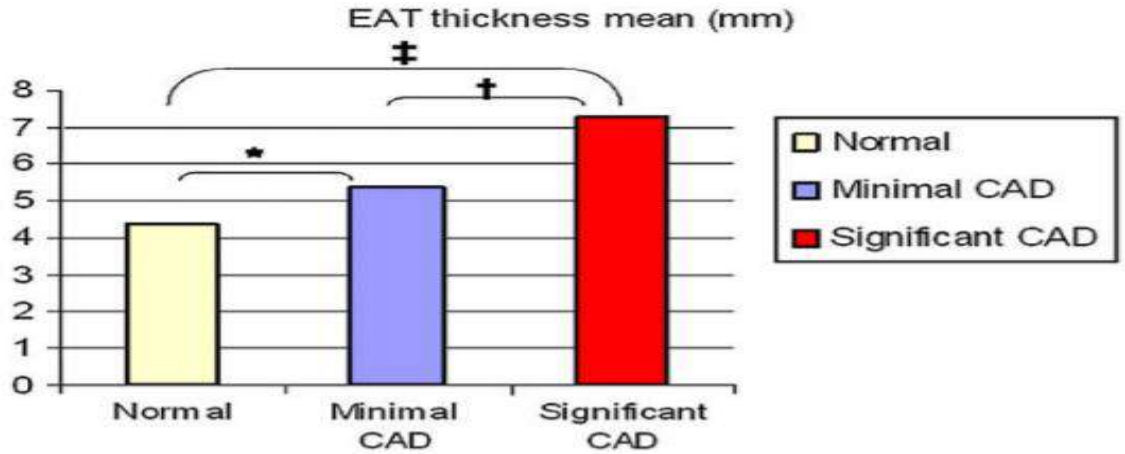


Figure 2 Association between epicardial adipose tissue thickness and severity of coronary artery disease (CAD) (*$P = 0.005$, minimal CADvs. normal; †$P < 0.001$, significant CADvs. minimal CAD; ‡$P < 0.001$, significant CADvs. normal).

Epikardiyal yağ kalınlığının 5.2 mm üzerinde olması: %85 duyarlılık, %81 özgünlük

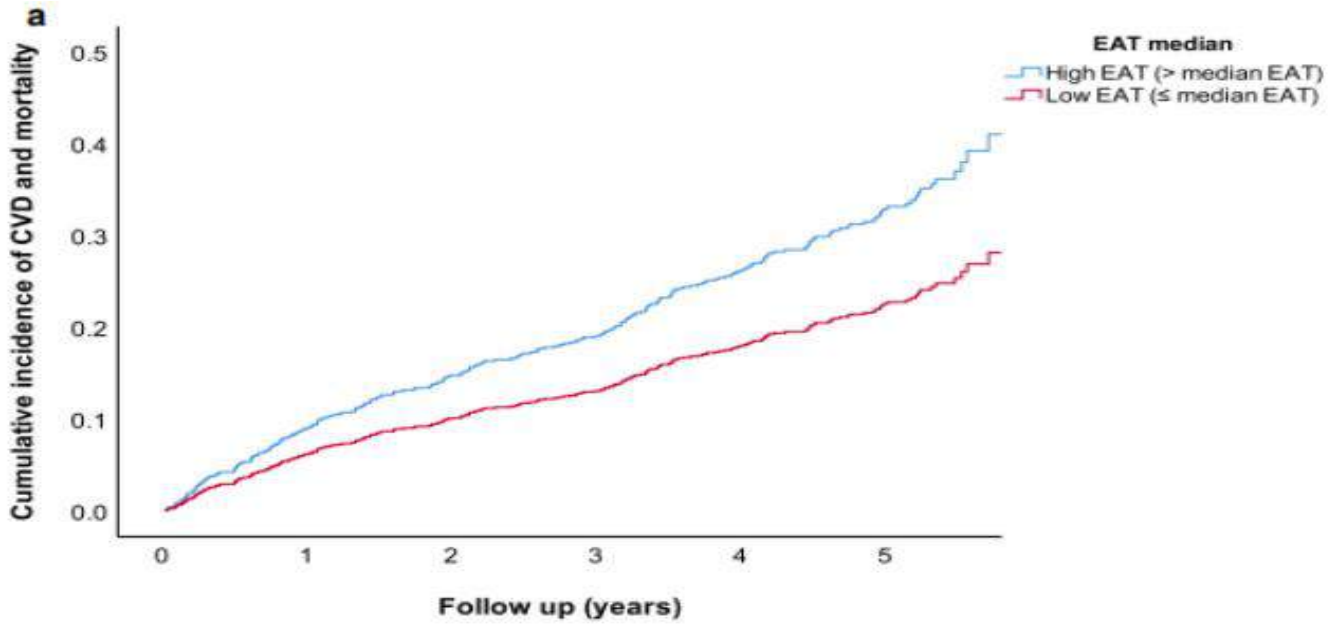
Christensen et al. Cardiovasc Diabetol (2019) 18:114
https://doi.org/10.1186/s12933-019-0917-y

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Epicardial adipose tissue predicts incident cardiovascular disease and mortality in patients with type 2 diabetes

Regitse H. Christensen[1,2*], Bernt Johan von Scholten[2], Christian S. Hansen[2], Magnus T. Jensen[3,4], Tina Vilsbøll[2,5], Peter Rossing[2,5] and Peter G. Jørgensen[4]

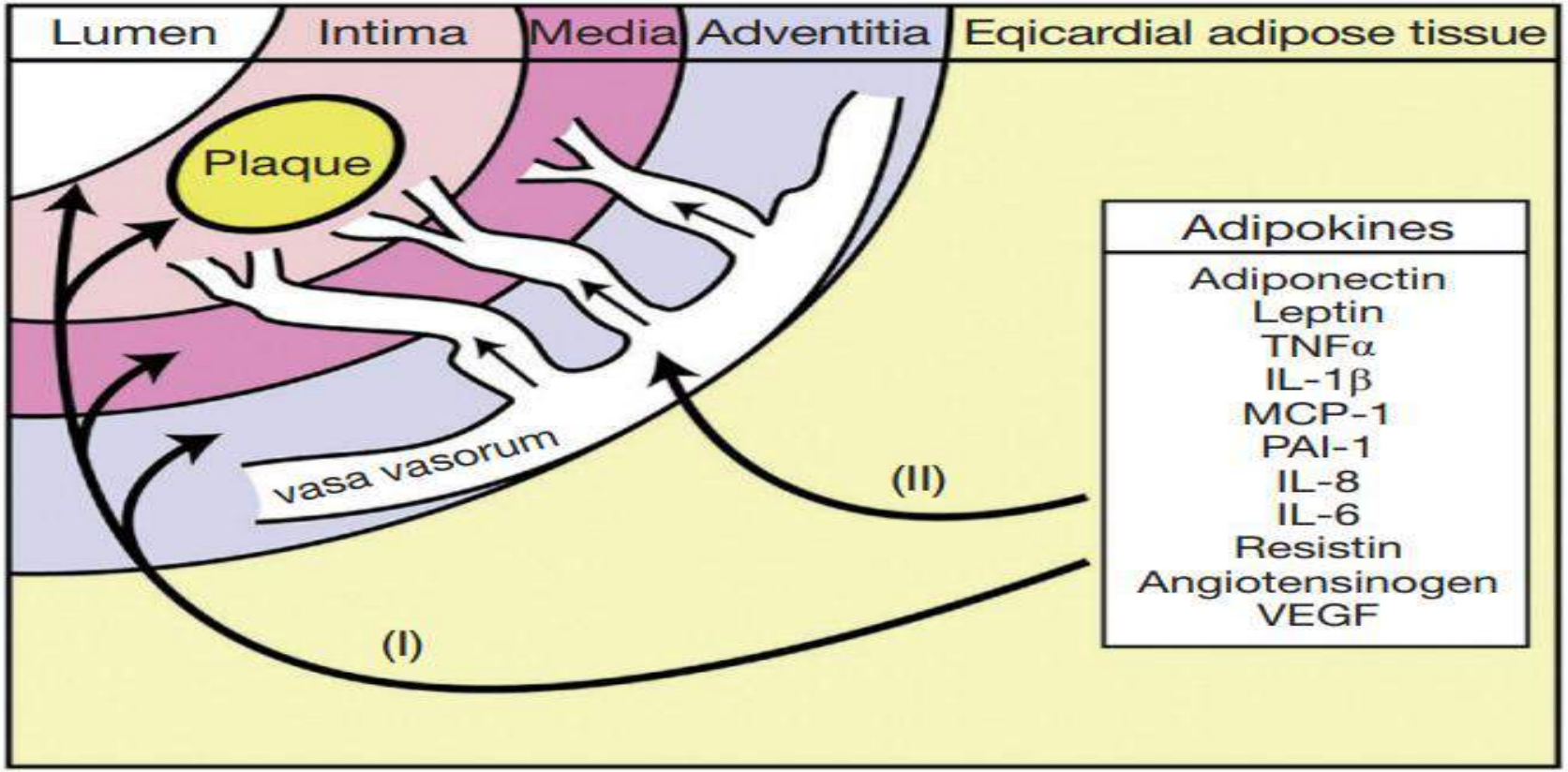


Review Article

Cardiovasc Diagn Ther 2014;4(6):416-429

Epicardial adipose tissue: far more than a fat depot

Andrew H. Talman[1], Peter J. Psaltis[1,2], James D. Cameron[1], Ian T. Meredith[1], Sujith K. Seneviratne[1], Dennis T. L. Wong[1,2]



❖ Talman AH et al. Cardiovasc Diagn Ther 2014;4:416-29.

González et al. Cardiovasc Diabetol (2017) 16:44
DOI 10.1186/s12933-017-0528-4

Cardiovascular Diabetology

REVIEW Open Access

Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes

N. González[1,2], Z. Moreno-Villegas[1], A. González-Bris[1], J. Egido[1,2] and Ó. Lorenzo[1,2*]

- Obezite ve ilişkili kardiyovasküler bozuklukların tedavisinde temel amaç visseral ve epikardiyal yağ dokusunda BYD ve KYD dengesini sağlamaktır.
- Visseral ve epikardiyal yağ dokusunda BYD artışı obezite ve ilişkili kardiyovasküler bozukluklarda artmış risk ile ilişkilidir. Bu dokunun azaltılması ya da KYD'na dönüştürülmesi yararlıdır.

Table 2 Non-pharmacological and pharmacological strategies to reduce the *WAT/BAT* ratio in VAT and EAT depots

Non-Pharmacological	Pharmacological
- Nutritional changes - Increased physical activity - Gene regulation . mRNA: UCP-1, CIDE-A, PRDM16, USF1 . miRNA: miR-26, miR-133, miR-125b-5p - *BAT* activation: β3-adrenergic, cold - *BAT* transplantation - Bariatric surgery: Roux-en-Y gastric bypass	- Metformin - PPARγ activators (rosiglitazone) - Anti-obesity drugs (naltroxene+bupropion, phentermine+topiramate) - Statins (atorvastatin) - GLP-1R agonists (exenatide, liraglutide) - DPP-4 inhibitors (sitagliptin)

❖ Gonzalez N et al. Cardiovasc Diabetol 2017;16:44.

Nutrition, Metabolism & Cardiovascular Diseases (2009) 19, 760—766

Comparison of epicardial, abdominal and regional fat compartments in response to weight loss

M.-K. Kim [a,*], K. Tanaka [a], M.-J. Kim [a], T. Matuso [a], T. Endo [a], T. Tomita [b], S. Maeda [a,c], R. Ajisaka [a]

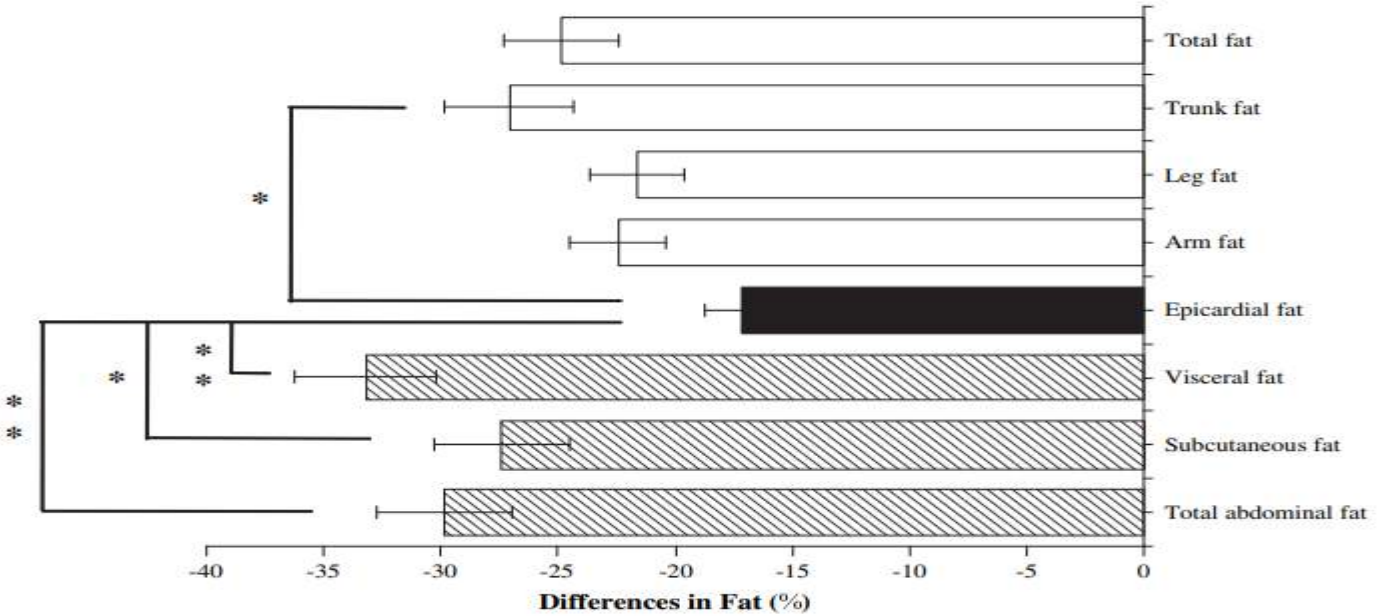


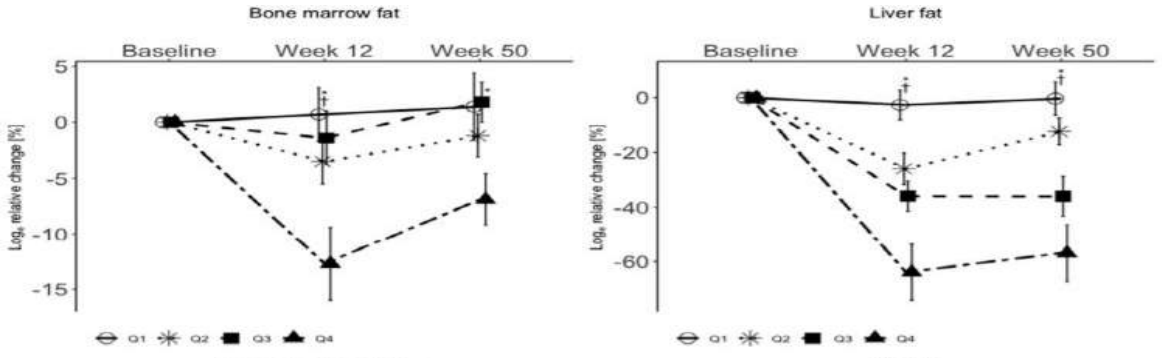
Figure 1 Changes in different adipose tissues of the body based on their anatomical location after the weight loss program. Percent changes in the regional, abdominal and epicardial fat tissues measured before and after the 12-week weight loss program. The graph shown indicates the mean ± SE. The white bars indicate analysis by DXA, black bars indicate analysis by echocardiography, and the shaded bars indicate analysis by CT. $^{*}P < 0.05$, $^{**}P < 0.001$.

Article

Nutrients **2020**, *12*, 1509; doi:10.3390/nu12051509

Changes in Bone Marrow Fat upon Dietary-Induced Weight Loss

Manuela Spurny [1], Yixin Jiang [1], Solomon A. Sowah [2], Ruth Schübel [1,2], Tobias Nonnenmacher [1], Robert Bertheau [1], Romy Kirsten [2], Theron Johnson [2], Jens Hillengass [3], Christopher L. Schlett [4], Oyunbileg von Stackelberg [1], Cornelia M. Ulrich [5], Rudolf Kaaks [2], Hans-Ulrich Kauczor [1], Tilman Kühn [2] and Johanna Nattenmüller [1,*]



5. Conclusions

In conclusion, BMF decreases significantly in overweight and obese, but metabolically healthy individuals after dietary-induced weight reduction of more than 7.5%. In our study, BMFC showed no stronger associations with inflammatory and metabolic biomarkers nor blood cell counts. However, our results underline the role of BMF as a metabolically active fat depot. In addition, as obesity is a risk factor for some malignancies and BMFC is linked to bone health, metabolism and haematological diseases, the role and a potential preventive capacity of reduced BMFC after weight loss should be evaluated in future studies.

Figure 2. Relative changes of BMFC, LFC, VAT and weight by weight loss quartiles.

❖ Spurny M et al. Nutrients 2020;12:1509.

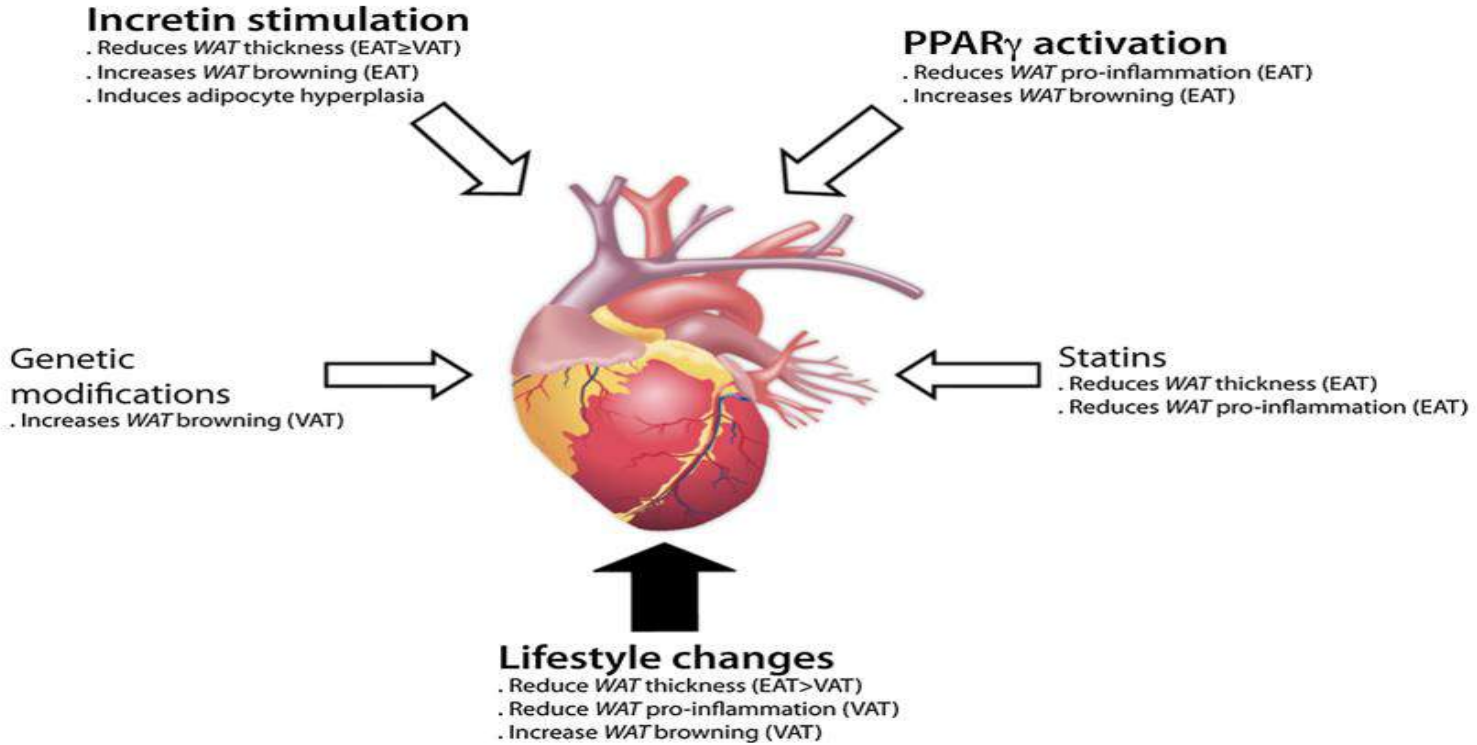


Fig. 2 Prospective fat-modulating interventions for cardiovascular dysfunction in obesity and T2DM. In addition to lifestyle modifications on diet and exercise, cardiovascular complications in patients with increased VAT and EAT may be treated with statins or genetic manipulations (focused on USF1, CIDE-A, PGC1a, UCP-1, PRDM-16 or miR-125b-5p) to decrease *WAT* thickness/pro-inflammation in EAT or increase *WAT* browning in VAT, respectively. More significant, PPARγ agonists could promote these effects particularly in EAT, and additionally, incretin stimulation might also induce adipocyte hyperplasia, and subsequent insulin sensitivity

❖ Gonzalez N et al. Cardiovasc Diabetol 2017;16:44.

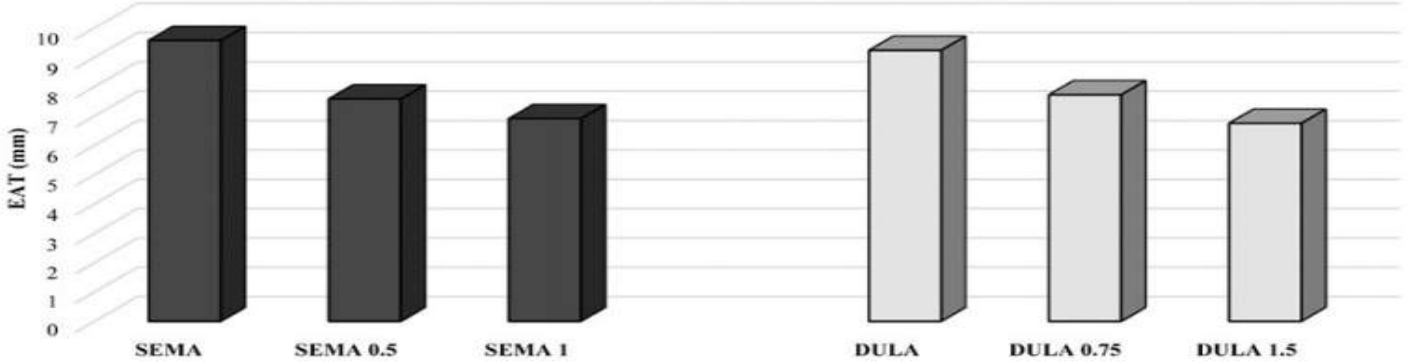
Effects of Semaglutide Versus Dulaglutide on Epicardial Fat Thickness in Subjects with Type 2 Diabetes and Obesity

Gianluca Iacobellis and Alexandra C. Villasante Fricke

April 2020 | Vol. 4, Iss. 4
Journal of the Endocrine Society | 1–9

Table 2. Changes of the Study Variables in the 3 Groups During the 12 Weeks

	Semaglutide Baseline n = 30	12 Weeks *n = 28*	*P*	Dulaglutide Baseline *n = 30*	12 Weeks *n = 28*	*P*	Metformin Baseline *n = 20*	12 Weeks *n = 18*	*P*
BMI (Kg/m2)	34.3 ± 5	33.8 ± 4	ns	36.5 ± 6	34 ± 5	ns	33.5 ± 6	32.1 ± 4	ns
HbA1c (%)	7.3 ± 1.2	6.9 ± 1.2	ns	8.2 ± 1.2	7.7 ± 1.1	ns	5.8 ± 0.6	5.9 ± 0.9	ns
SBP (mmHg)	132 ± 13	131 ± 14	ns	127 ± 18	126 ± 16	ns	123 ± 15	127 ± 17	ns
DBP(mmHg)	79.5 ± 8	81 ± 8	ns	76.8 ± 13	78 ± 9	ns	77.5 ± 9	76 ± 10	ns
HR (bpm)	79 ± 10	81 ± 11	ns	83 ± 13	79 ± 15	ns	75 ± 13	77 ± 16	ns
LDL (mg/dl)	99 ± 41	78 ± 30	ns	87 ± 33	78 ± 41	ns	116 ± 36	89 ± 17	< 0.05
HDL(mg/dl)	45 ± 16	44 ± 16	ns	43 ± 15	42 ± 13	ns	47 ± 11	55 ± 23	ns
EAT (mm)	9.5 ± 2.6	7.5 ± 2	< 0.01	9.3 ± 2.2	7.7 ± 2.2	< 0.01	7.1 ± 2.1	7.1 ± 2.2	ns



Sato et al. Cardiovasc Diabetol (2018) 17:6
https://doi.org/10.1186/s12933-017-0658-8

Cardiovascular Diabetology

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The effect of dapagliflozin treatment on epicardial adipose tissue volume

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Table 5 Change rate of adipose-associated markers after treatment

	Dapagliflozin (n = 20)	Conventional therapy (n = 20)	p value, dapagliflozin vs. conventional
ΔEAT volume (cm^3)	− 16.4 ± 8.3**	4.7 ± 8.8	0.01
ΔTNF-α (pg/ml)	− 0.5 ± 0.7**	0.03 ± 0.3	0.03
ΔPAI-1 (ng/ml)	− 10.1 ± 18.8*	− 2.0 ± 9.7	0.18

EAT epicardial adipose tissue, *TNF-α* tumor necrosis factor-α, *PAI-1* plasminogen activator inhibitor-1

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Targeting epicardial adipose tissue with exercise, diet, bariatric surgery or pharmaceutical interventions: A systematic review and meta-analysis

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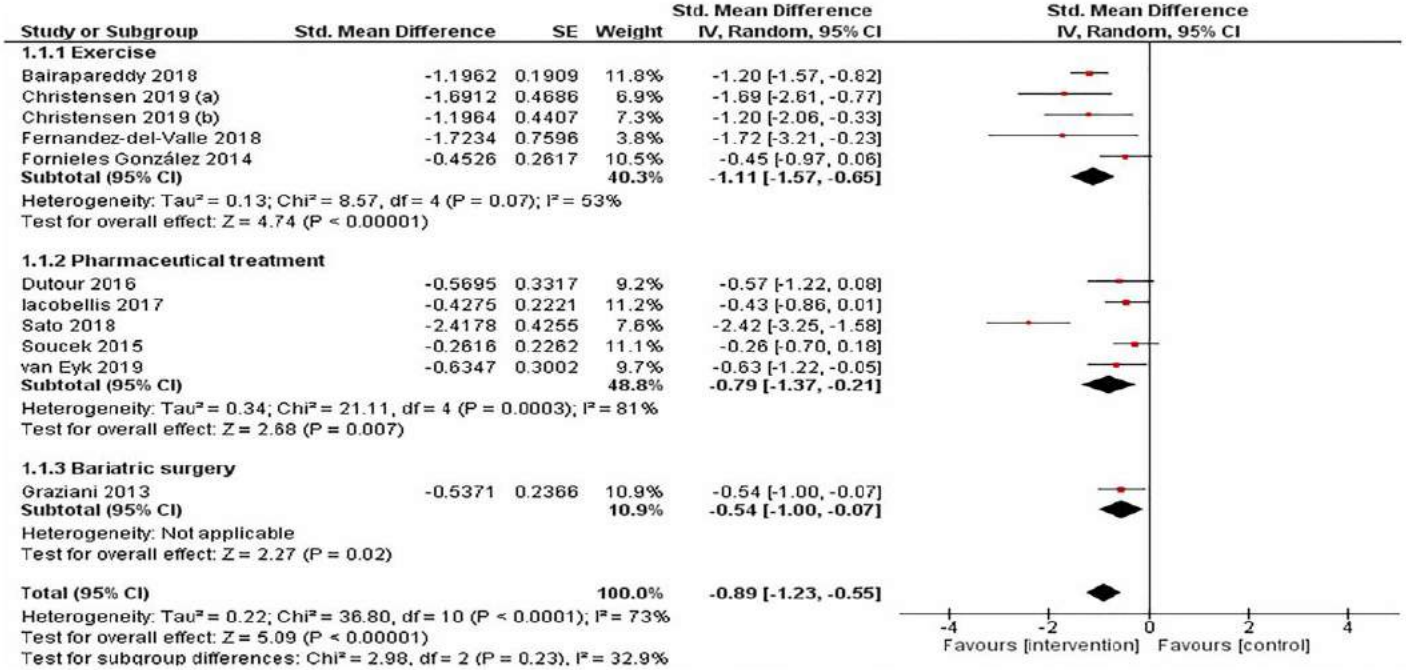

FIGURE 3 Forest plot depicting the effect of the interventions pooled or divided by subgroup on change in epicardial adipose tissue. Plots depict the effect size (std. mean difference) and 95% CI for the individual studies and the pooled estimate. Std, standard; IV, inverse; SE: standard error; CI, confidence interval

Epicardial adipose tissue: an emerging biomarker of cardiovascular complications in type 2 diabetes?

Regitse Højgaard Christensen, Bernt Johan von Scholten, Louise Lang Lehrskov, Peter Rossing and Peter Godsk Jørgensen

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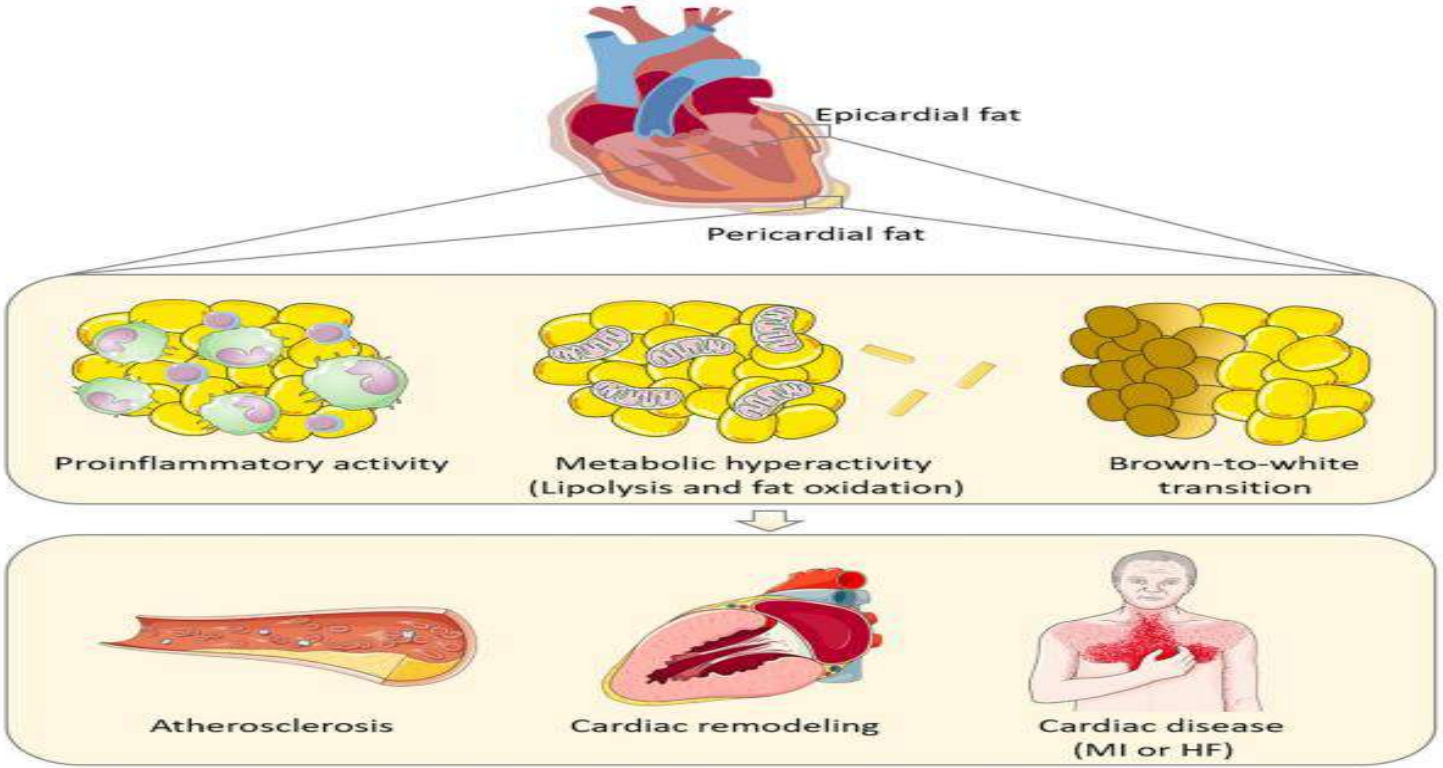

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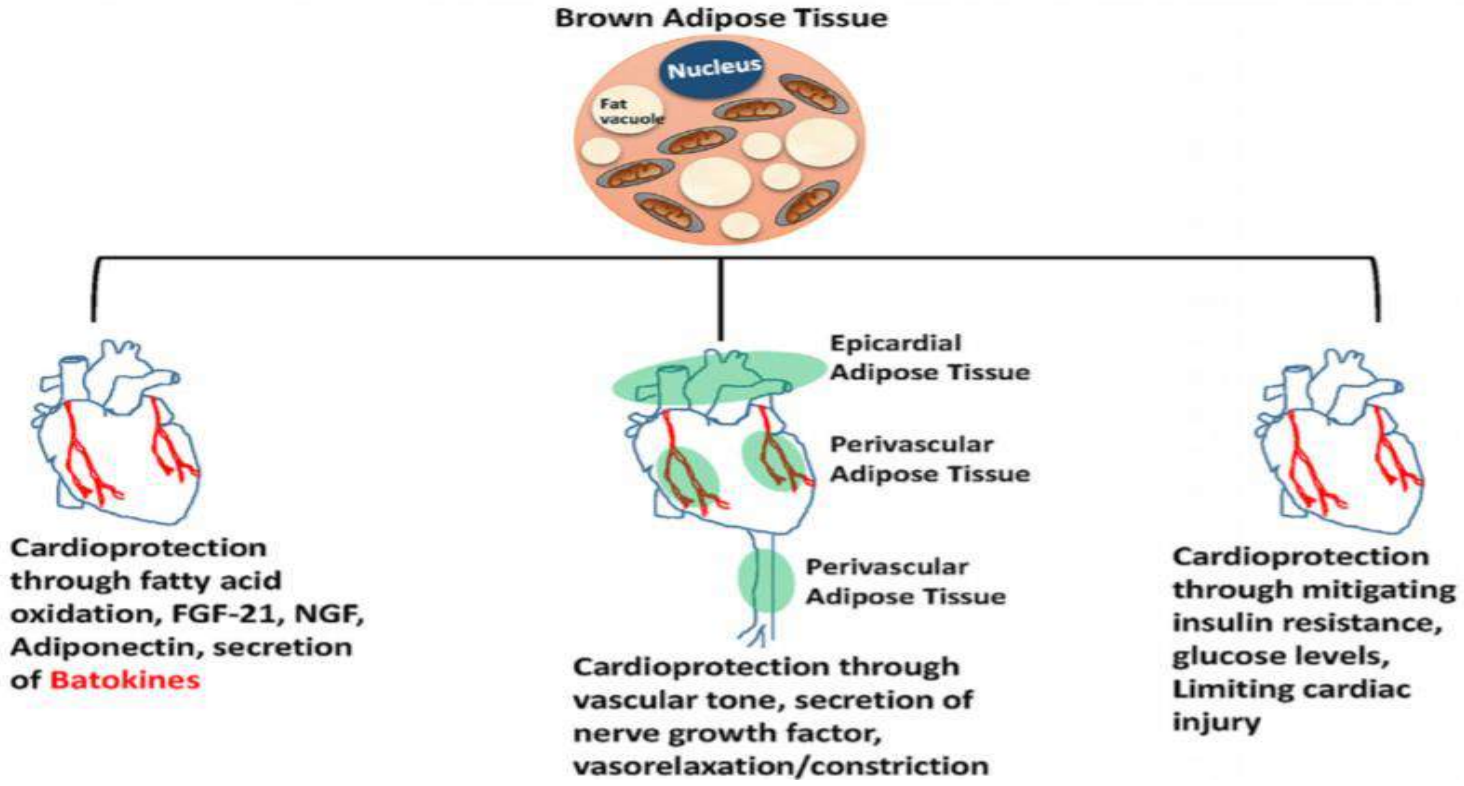
NEVENA JEREMIC, PANKAJ CHATURVEDI, and SURESH C. TYAGI*



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