The Effect on Cardiac Structure and Function of SGLT2i and GLP-1 RA in Experimental Animal Models

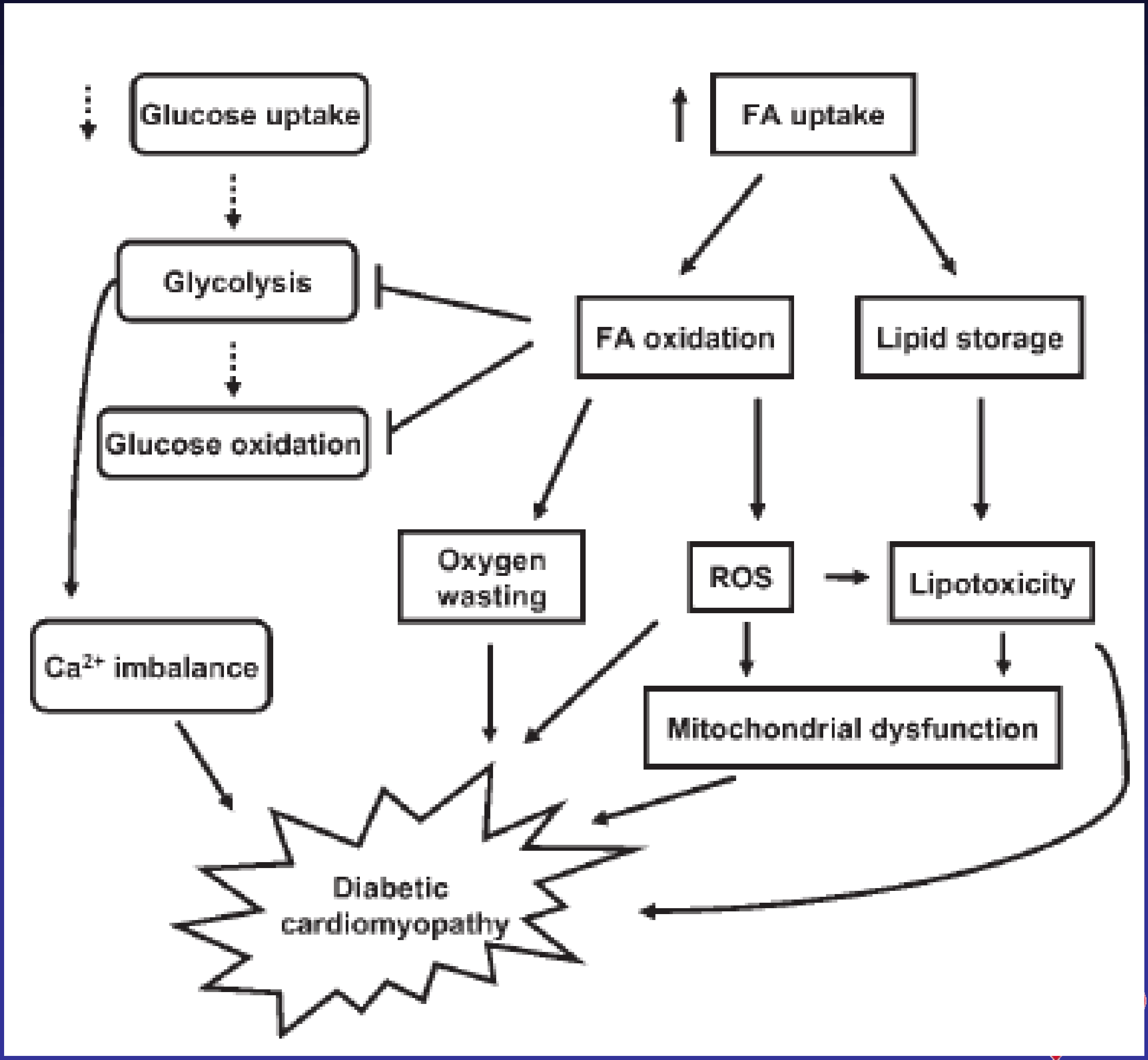
Annual Meeting of the Working Group on Myocardial & Pericardial Diseases
Tel Aviv 30 June 2022

Michael Arad MD
The Leviev Heart Center
Sheba Medical Center and Tel Aviv University, Israel

Changes in cardiac metabolism in diabetes

An & Rodrigues, Am J Physiol 2006

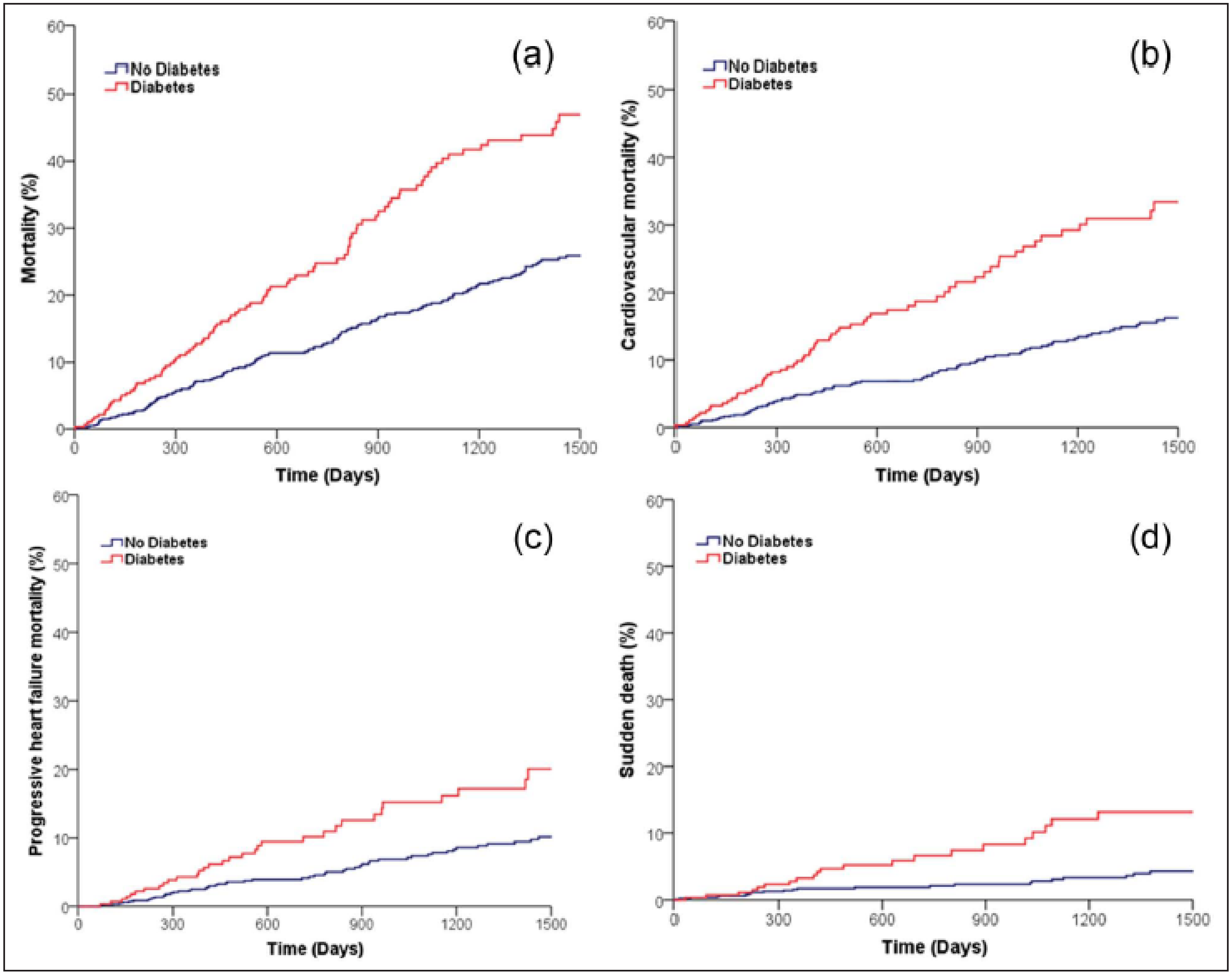
1. Elevated serum & myocardial FA,TG
2. Decreased glucose uptake & utilization
3. Hyperglycemia
4. ± Hyperinsulinemia



Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology

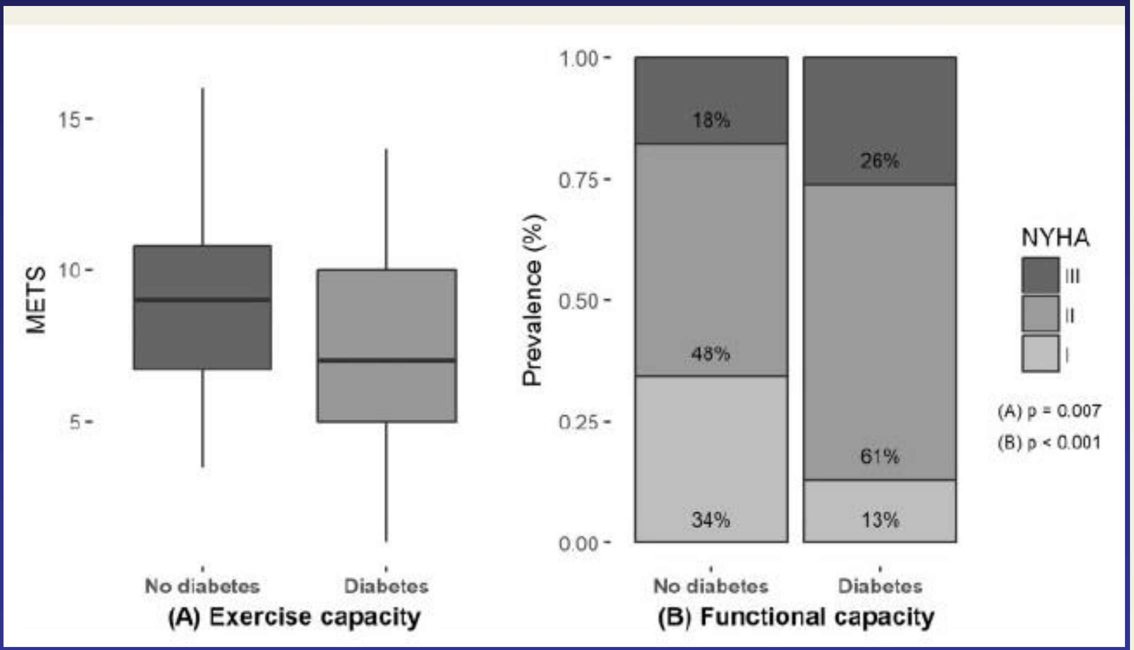
Cubbon RM, et al. Diabetes & Vascular Disease Research 2013

1091 Heart Failure patients. 280 (26%) had Diabetes Mellitus on recruitment



In Hypertrophic Cardiomyopathy, DM was associated with diastolic dysfunction, worse functional class, atrial fibrillation and adverse prognosis.

Wasserstrum and Arad et al, Eur Heart J 2019



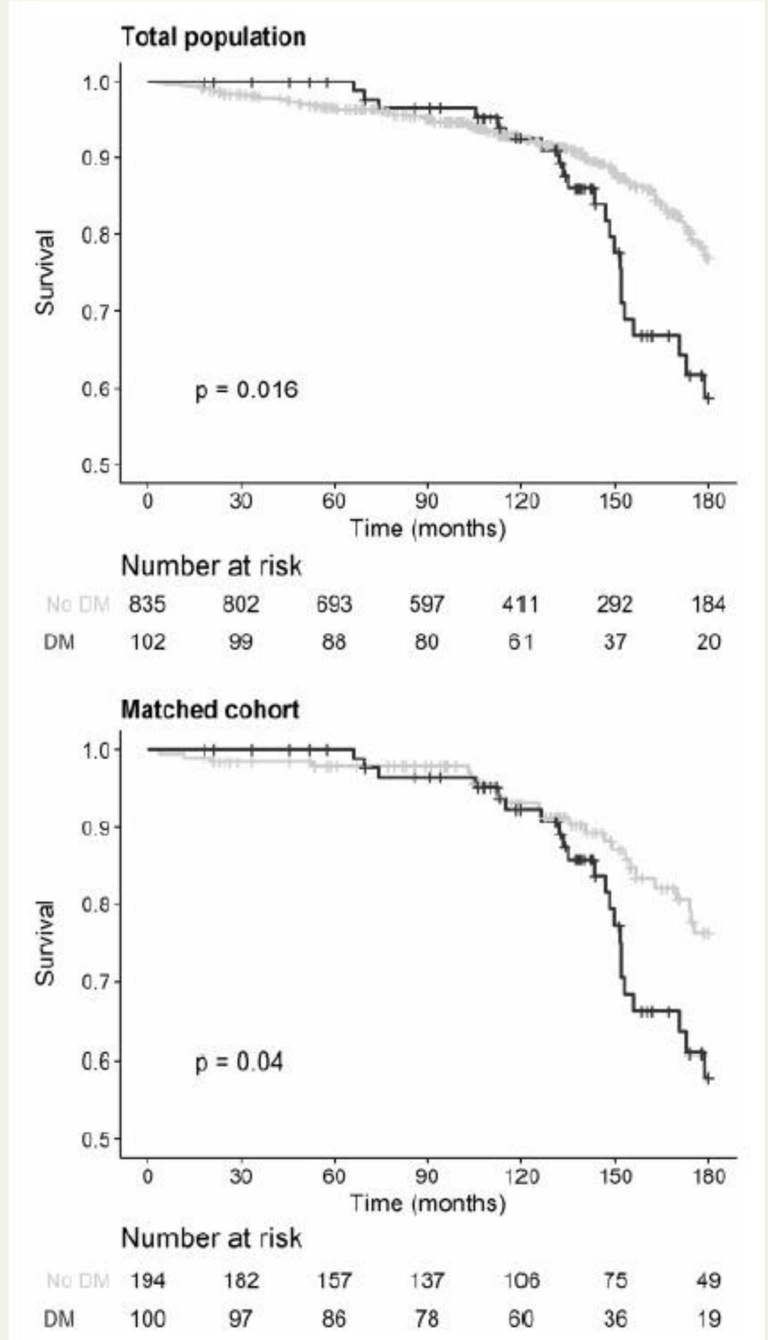


Figure 2 Fifteen-year survival.

Sheba Medical Center
Tel Hashomer

Diabetic CMP – fact or fiction?

Diabetic CMP is a distinct entity characterized by the presence of abnormal myocardial performance or structure, in the absence of epicardial coronary artery disease, hypertension and significant valvular disease.

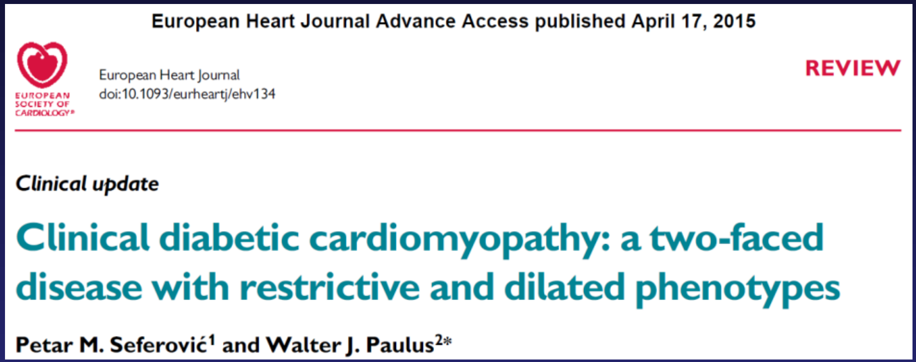
Aneja, Am J Med 2008

Maisch, Herz 2011

Rare as «stand alone» common as «add on»

Stages of diabetic cardiomyopathy

- Increased cardiomyocyte stiffness + hypertrophy → diastolic dysfunction
- Changes in the interstitium:
  - Inflammation
  - Increased sensitivity to Angiotensin II
  - AGE → collagen crosslinking
  - Fibrosis
- Systolic dysfunction and overt Heart Failure
- Aggravation by hypertension, coronary disease


European Heart Journal Advance Access published April 17, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv134

EUROPEAN SOCIETY OF CARDIOLOGY®

REVIEW

Clinical update

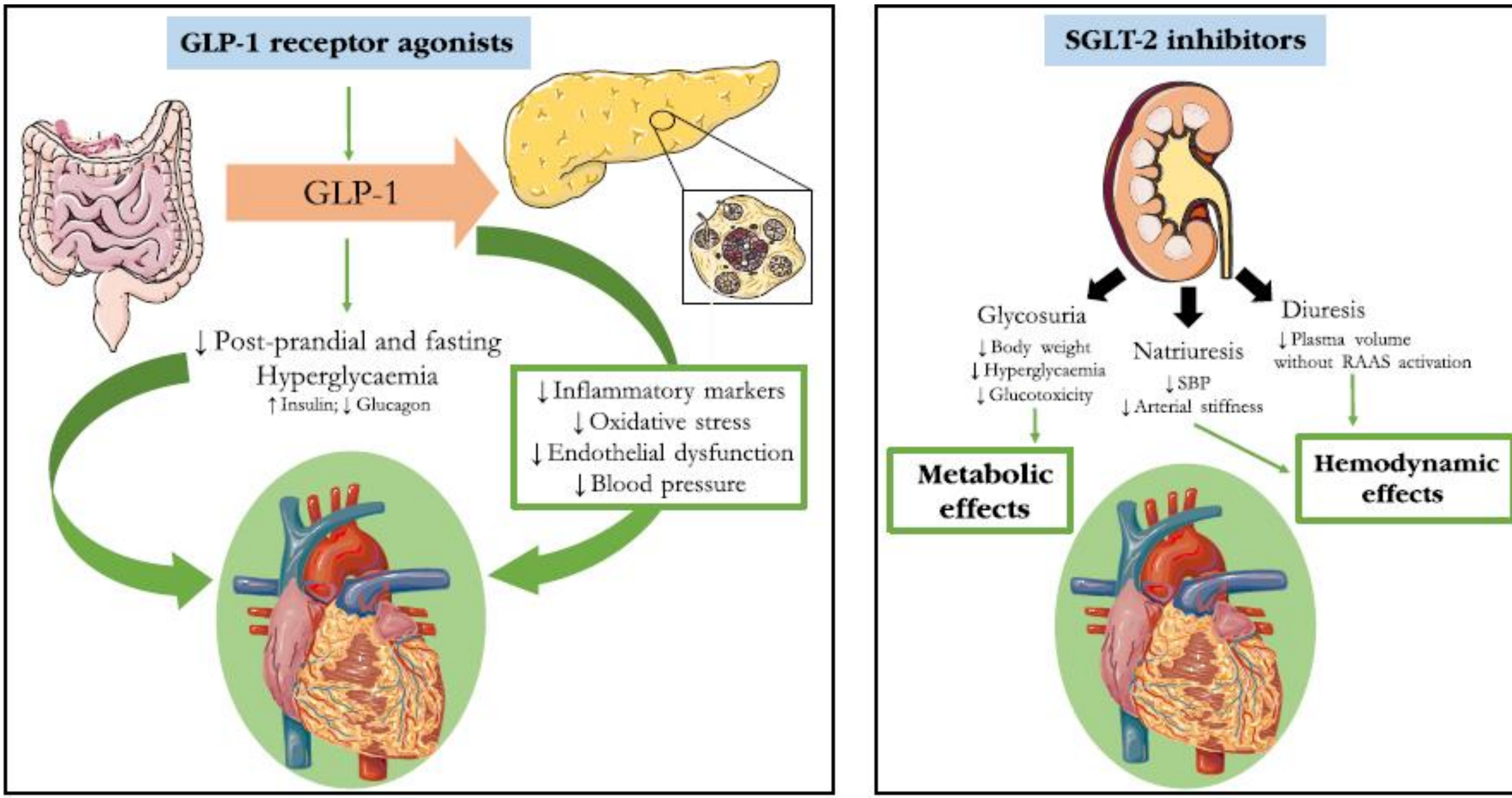
Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes

Petar M. Seferović[1] and Walter J. Paulus[2]*

doi: 10.1111/joim.12890

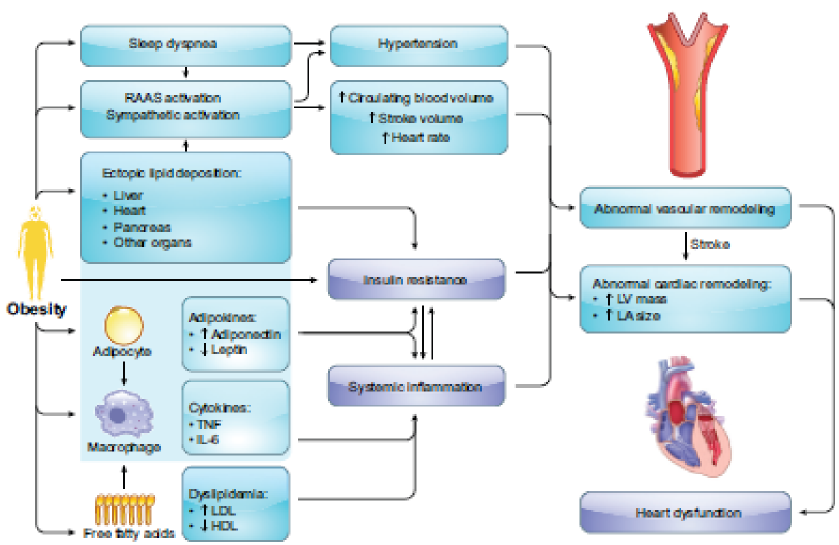
Pharmacologic strategies to reduce cardiovascular disease in type 2 diabetes mellitus: focus on SGLT-2 inhibitors and GLP-1 receptor agonists

A. Bonaventura[1,2], S. Carbone[2], D. L. Dixon[3], A. Abbate[2] & F. Montecucco[4,5]



american physiological society
PHYSIOLOGICAL REVIEWS
REN ET AL., 2021, *Physiol Rev* 101: 1745–1807
REVIEW ARTICLE

OBESITY CARDIOMYOPATHY: EVIDENCE, MECHANISMS, AND THERAPEUTIC IMPLICATIONS



AUTHORS

Jun Ren, Ne N. Wu, Shuyi Wang, James R. Sowers, Yingmei Zhang

CORRESPONDENCE

jren_aldh2@outlook.com; zhangym197951@126.com

KEY WORDS

cardiovascular disease; glucotoxicity; heart; inflammation; lipotoxicity; obesity; therapy

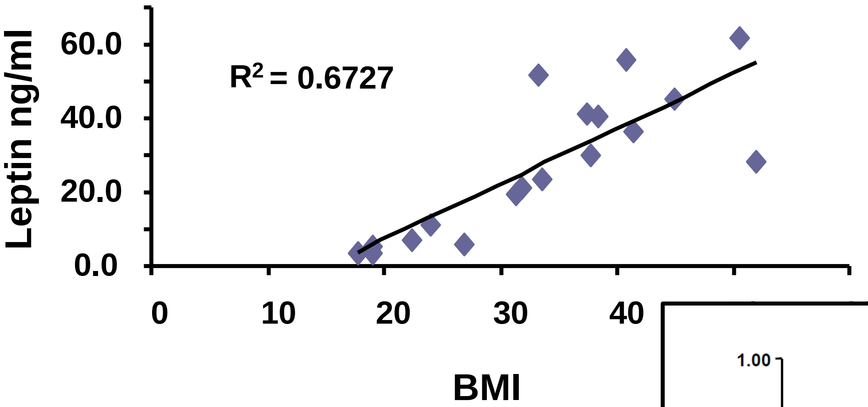
Contemporary understanding of the mechanisms underlying obesity cardiomyopathy include metabolic disturbances (insulin resistance, abnormal glucose transport, increased FAs, lipotoxicity and amino acid derangement), changes in intracellular Ca2 homeostasis, oxidative stress, autophagy dysregulation, myocardial fibrosis, cardiac autonomic neuropathy, inflammation, small coronary vessel disease, impaired coronary flow reserve, and coronary artery endothelial dysfunction.

In addition, epigenetic modifications also participate in the etiology of obesity cardiomyopathy.

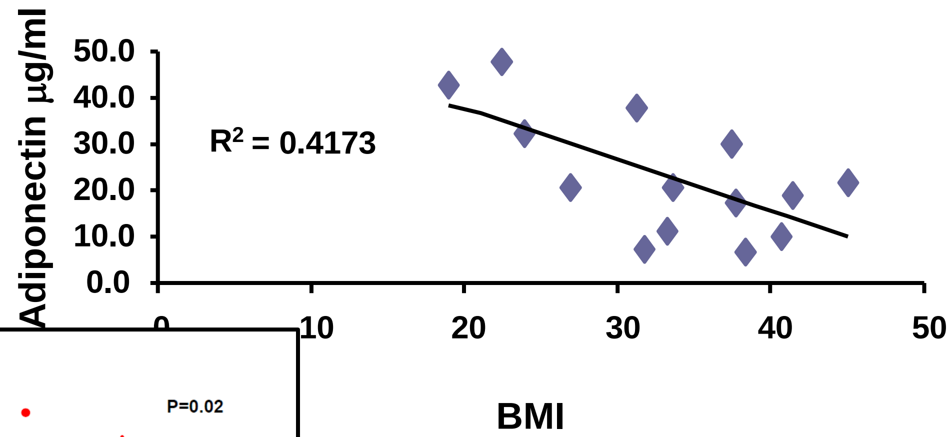
Ample evidence has been engaged toward the management of obesity cardiomyopathy, although effective and targeted medications and procedures are still lacking. Non-pharmacological approaches such as lifestyle modification (e.g., exercise and diet control) may benefit heart health …

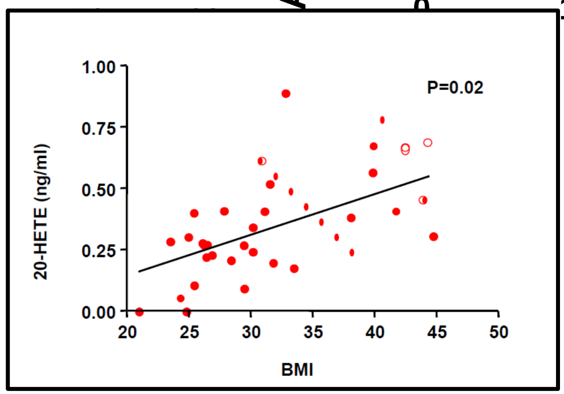
Effect of BMI on Cytokine Levels

A) Leptin as a function of BMI

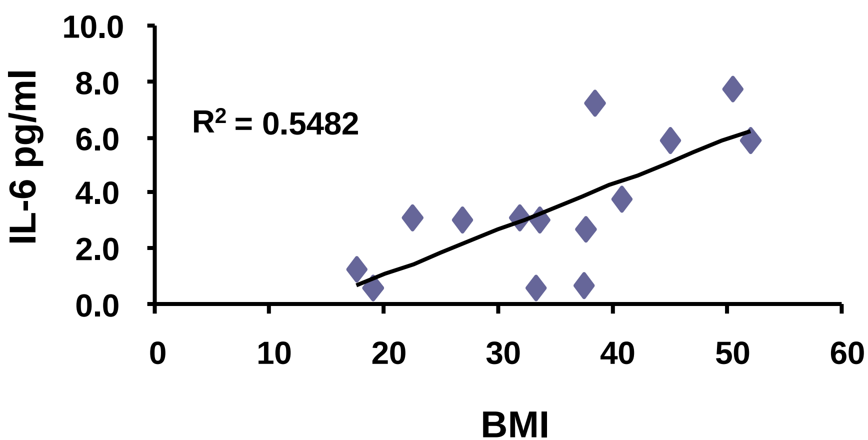


B) Adiponectin as a function of BMI

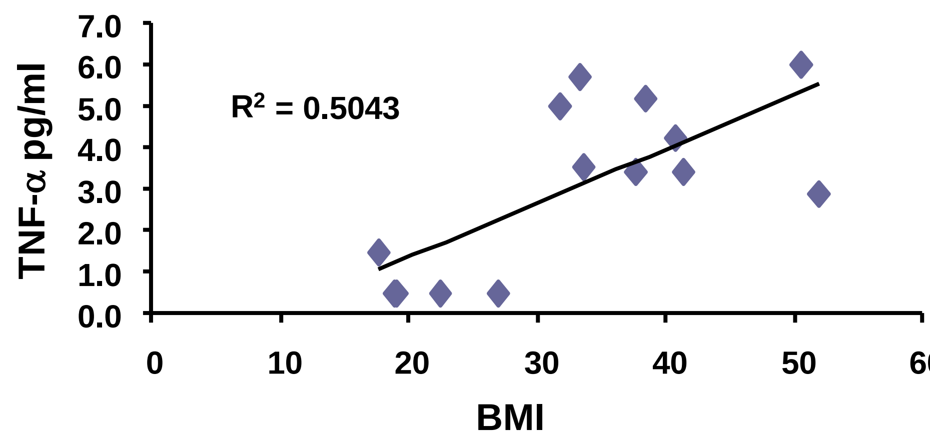


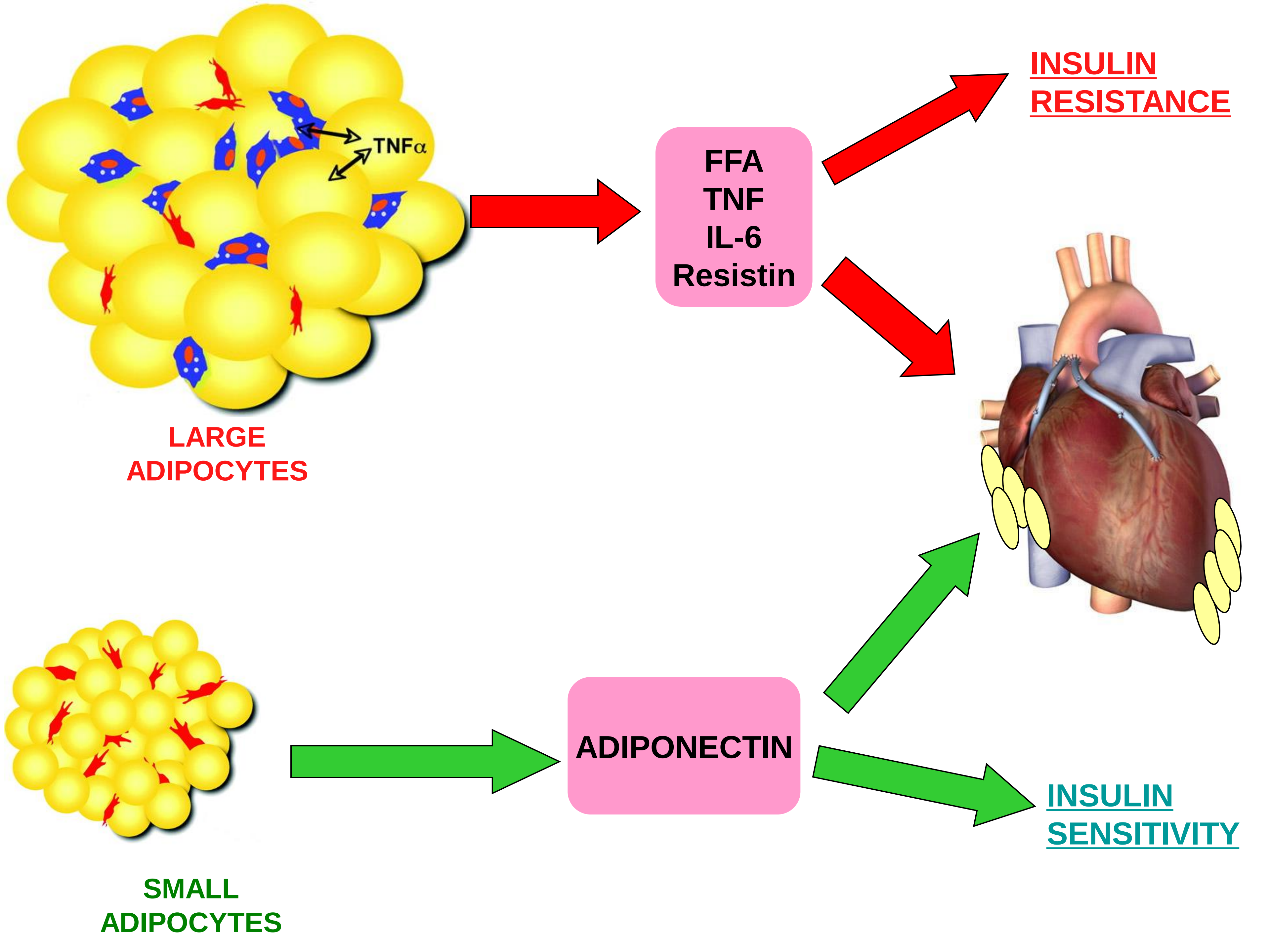


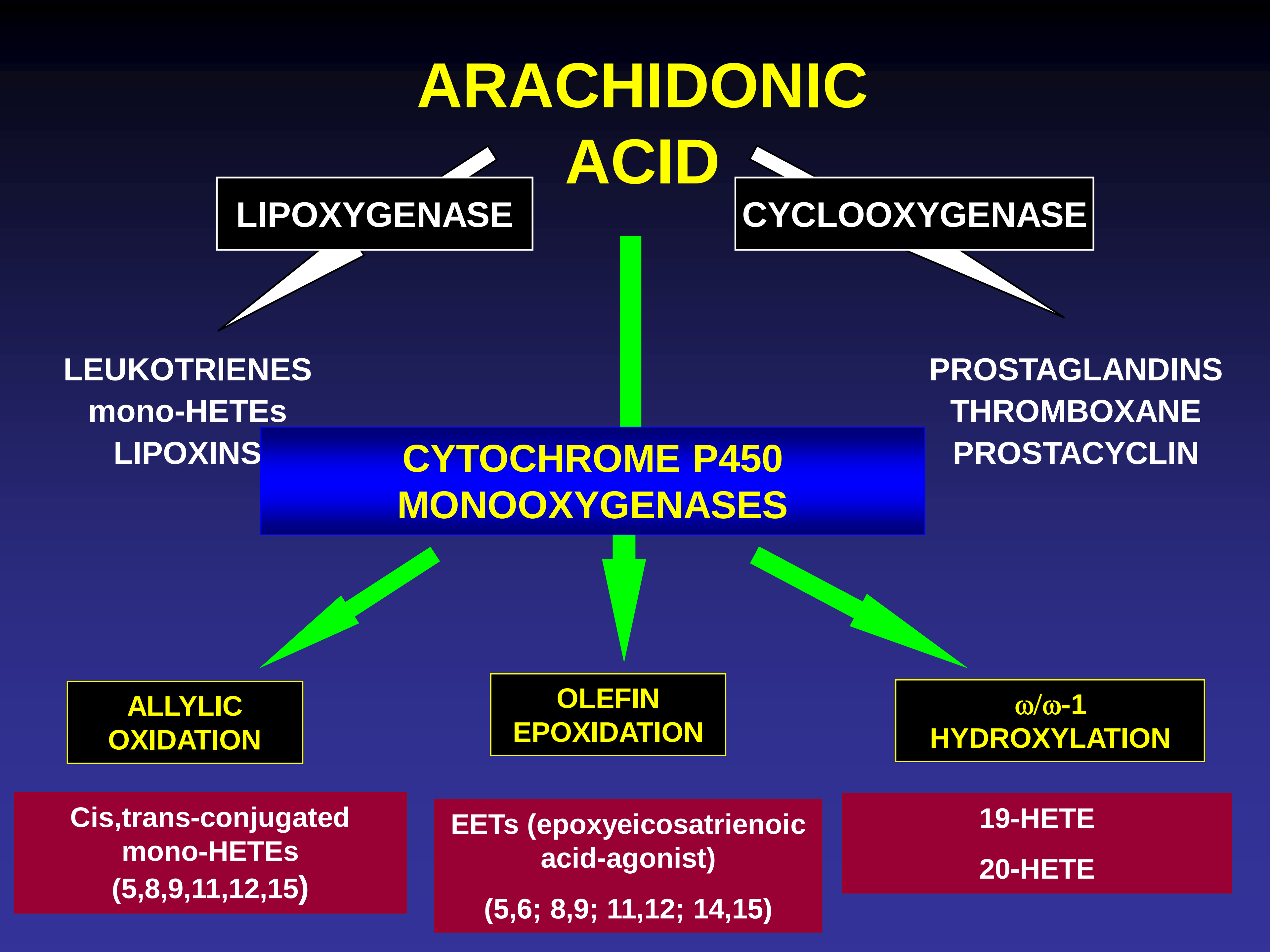
A) IL-6 as a function of BMI



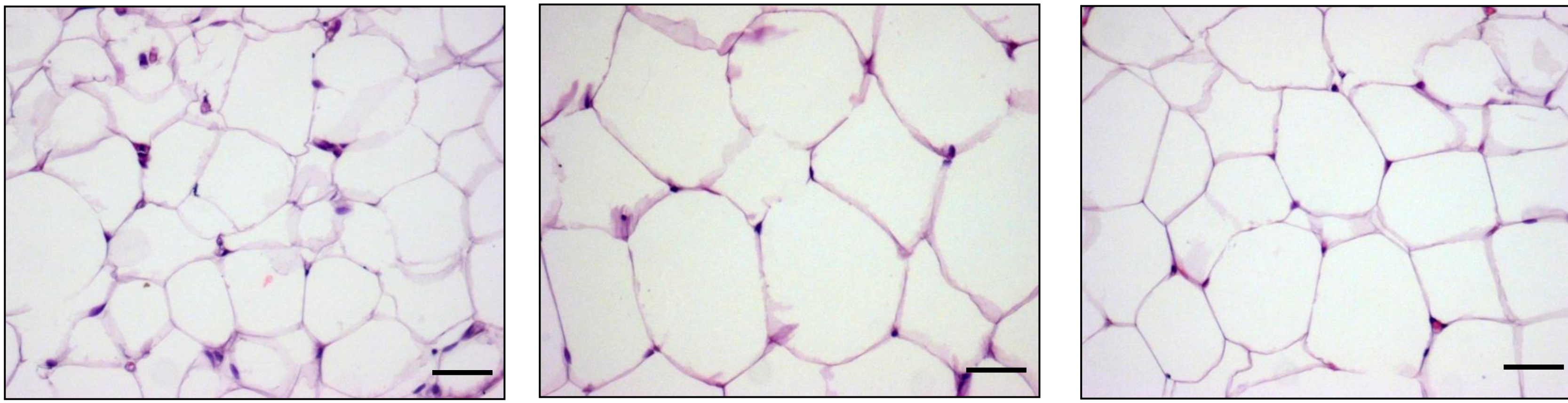
B) TNFα as a function of BMI



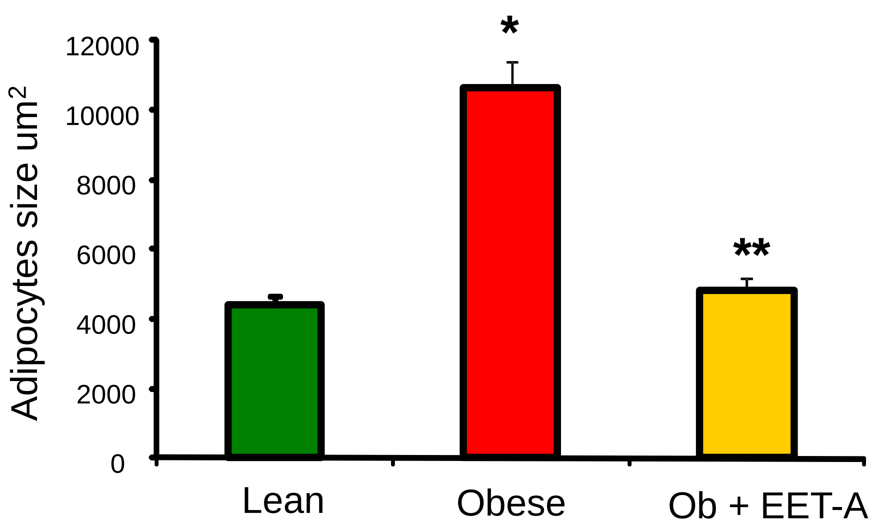

TNFα
FFA
TNF
IL-6
Resistin
INSULIN
RESISTANCE
LARGE
ADIPOCYTES
ADIPONECTIN
INSULIN
SENSITIVITY
SMALL
ADIPOCYTES

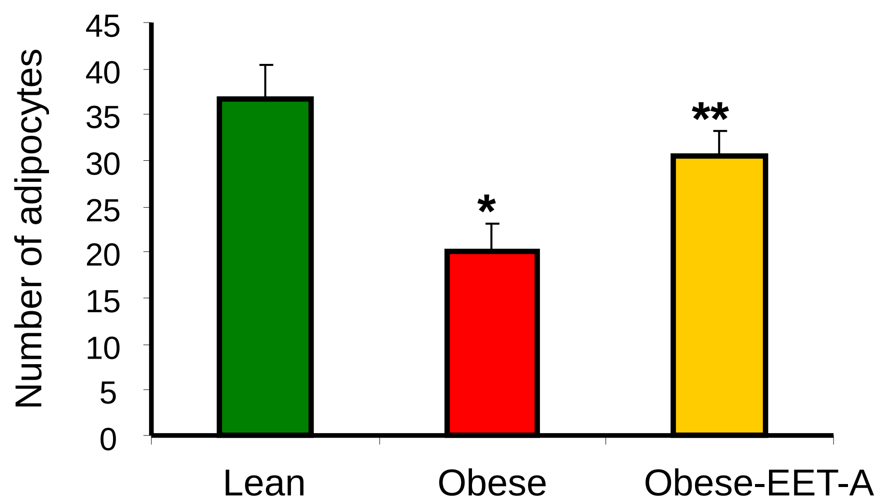

ARACHIDONIC ACID
LIPOXYGENASE
CYCLOOXYGENASE
LEUKOTRIENES
mono-HETEs
LIPOXINS
PROSTAGLANDINS
THROMBOXANE
PROSTACYCLIN
CYTOCHROME P450 MONOOXYGENASES
ALLYLIC OXIDATION
OLEFIN EPOXIDATION
ω/ω-1 HYDROXYLATION
Cis,trans-conjugated mono-HETEs (5,8,9,11,12,15)
EETs (epoxyeicosatrienoic acid-agonist)
(5,6; 8,9; 11,12; 14,15)
19-HETE
20-HETE

Induction of HO-1 by EET-A Decreases Adipocyte Size (VAT)



Lean **Obese** **Obese –EET-A**

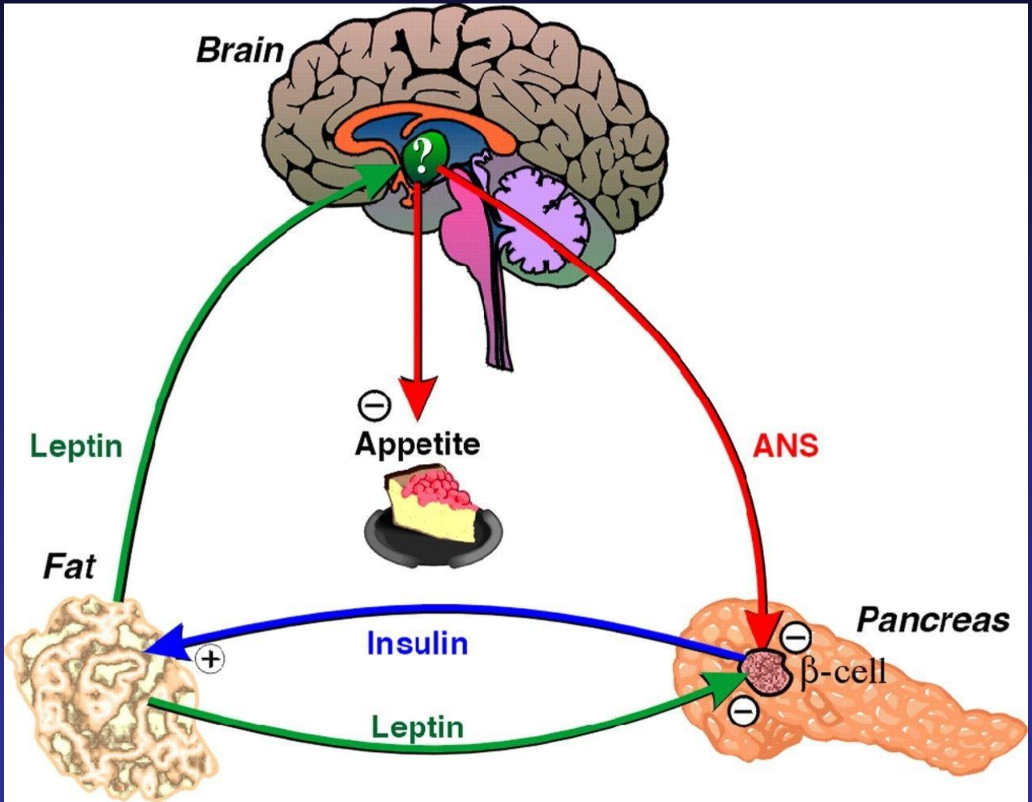


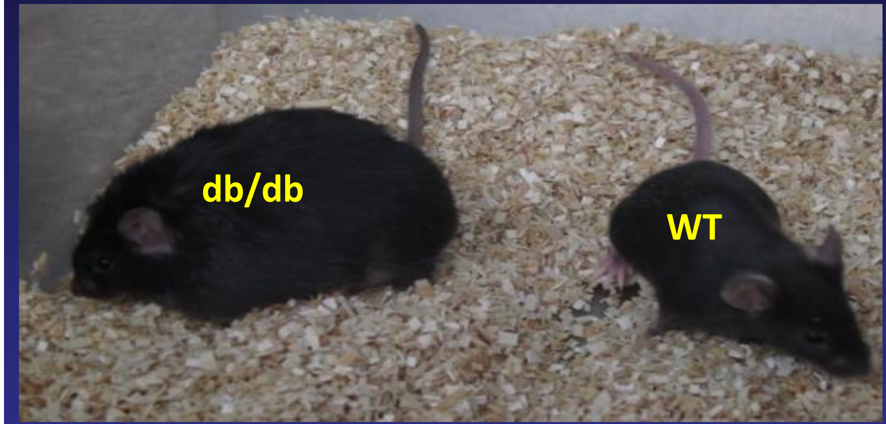


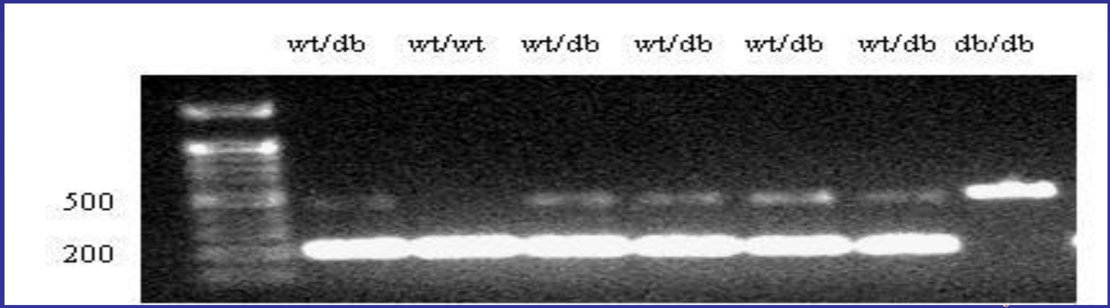
The Leviev Heart Center

Modelling diabetic/obesity cardiomyopathy

Deficiency of leptin receptor in db/db mice leads to obesity and diabetes
High fat diet or another stress are needed to create profound CMP

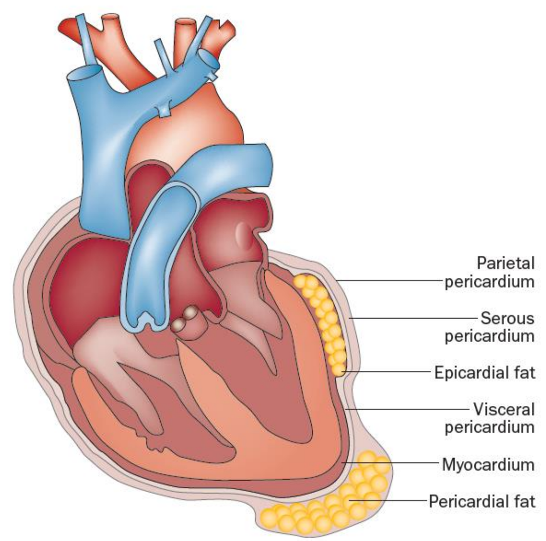




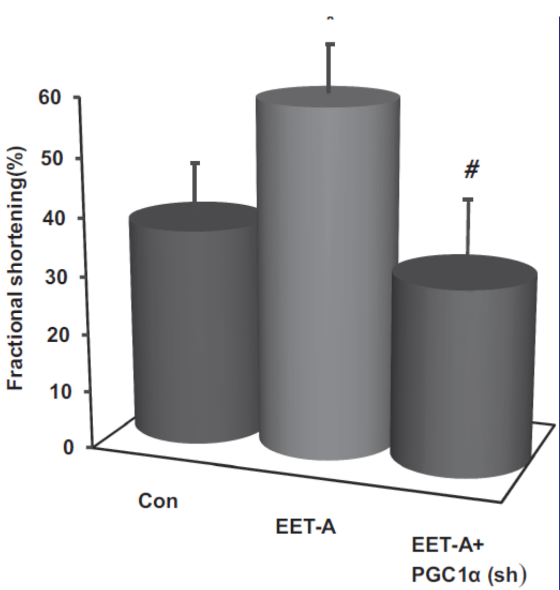


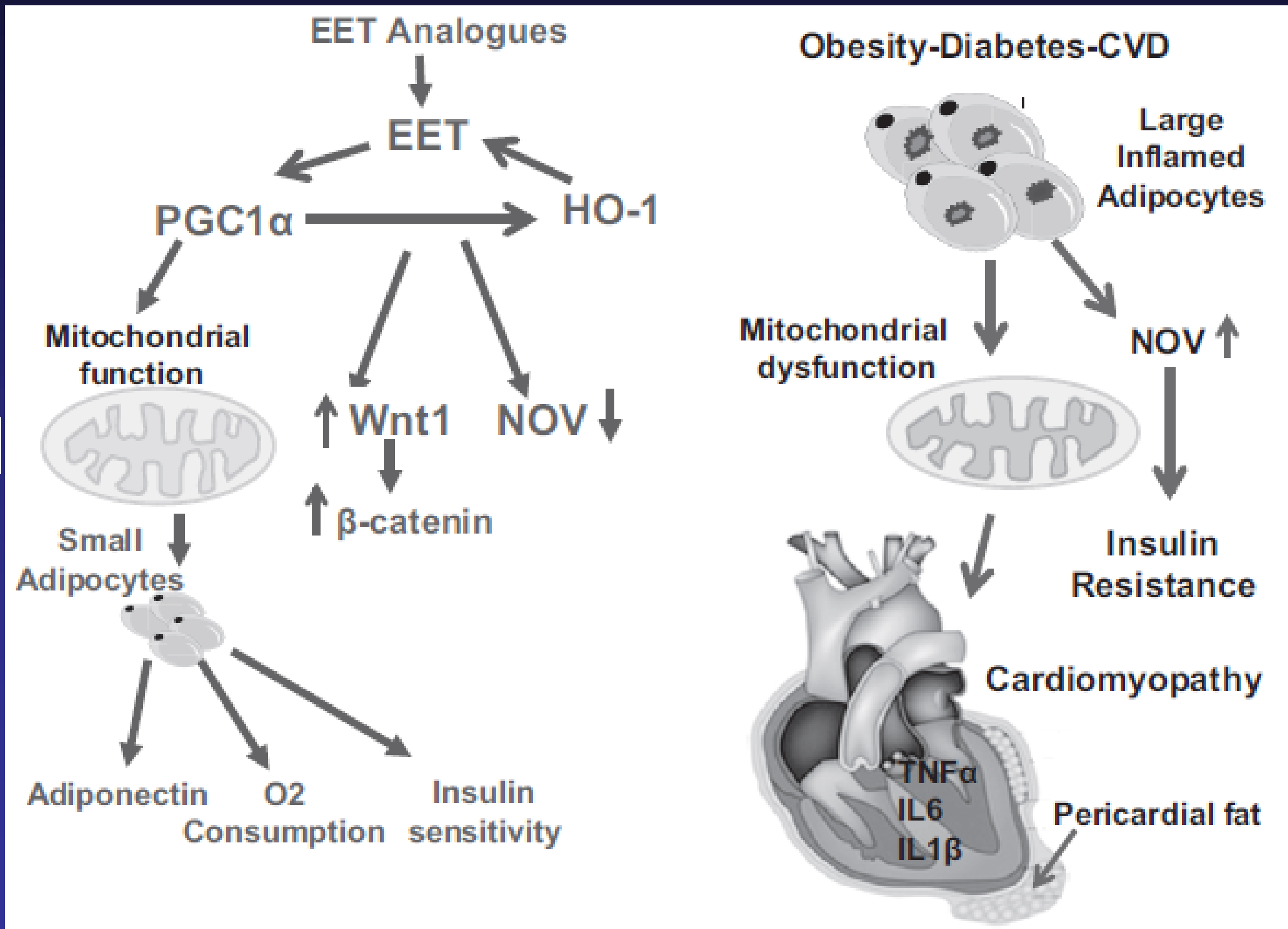
EET intervention on Wnt1, NOV, and HO-1 signaling prevents obesity-induced cardiomyopathy in obese mice

Cao et al, Am J Physiol 2017



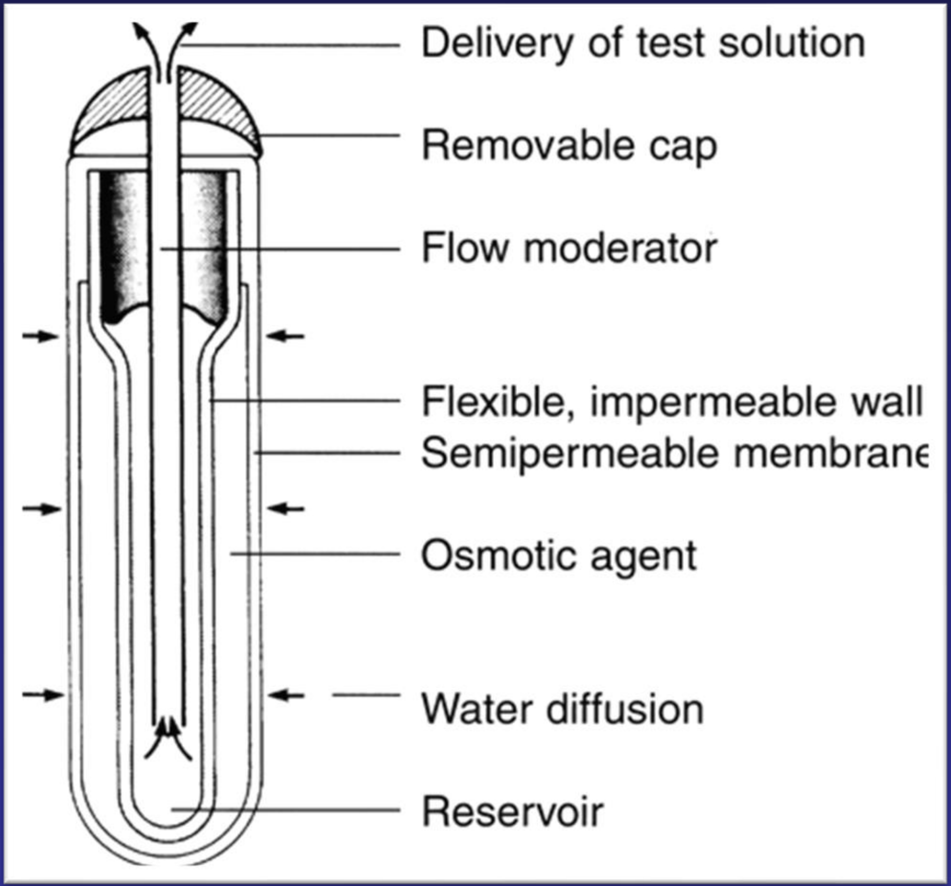
LV function in db/db mice on HF diet





2. Development of cardiomyopathy was accelerated by Angiotensin II (AT) stress

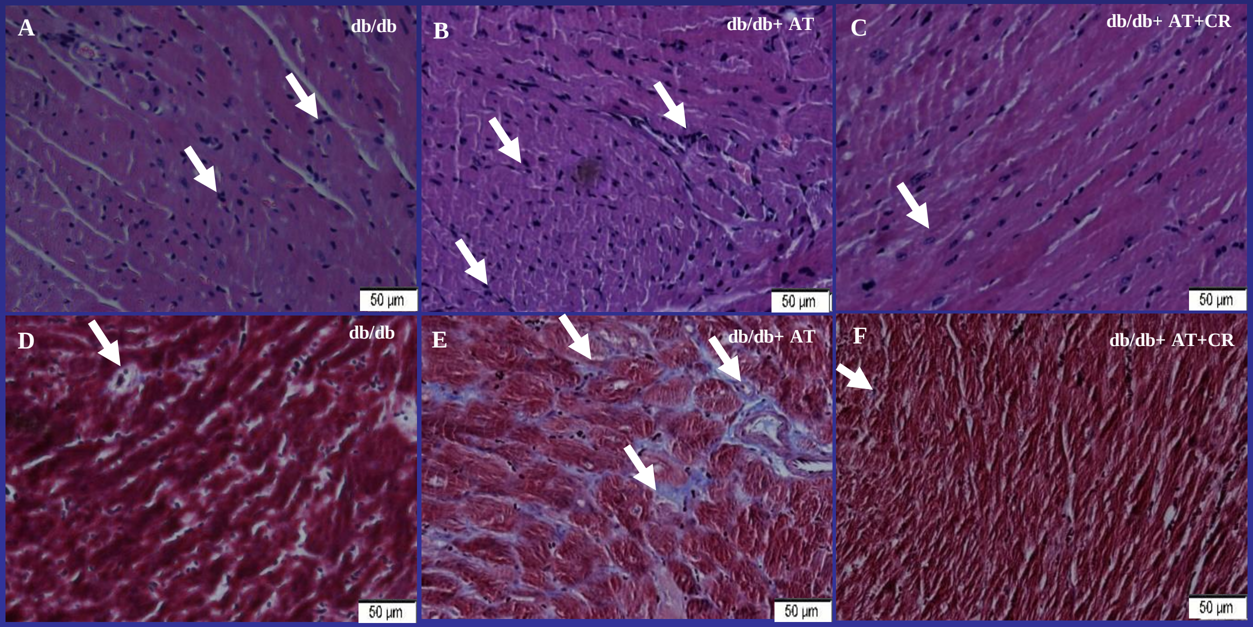
- AngiotensinII is administrated subcutaneously via ALZET osmotic pump at the rate of 1000ng/kg/min.



The protective effect of caloric restriction

Table 1: Physiological and metabolic biochemical markers

	db/db n=6	db/db+AT n=5	db/db+AT+CR n=5
Body Weight (g)	40.7±9.7	40.3±5.3	33.1±6.7[#&]
Heart Weight (mg)	117±20	163±30[#]	139±20[&]
Glucose (mg/dL)	617±93	658±107	531±127[&]
Cholesterol (mg/dL)	112±21	199±91[#]	118±25[&]
HDL (mg/dL)	112±26	188±74[#]	103±18[&]



Caloric restriction protects from diabetic cardiomyopathy

Cardiac function and dimensions

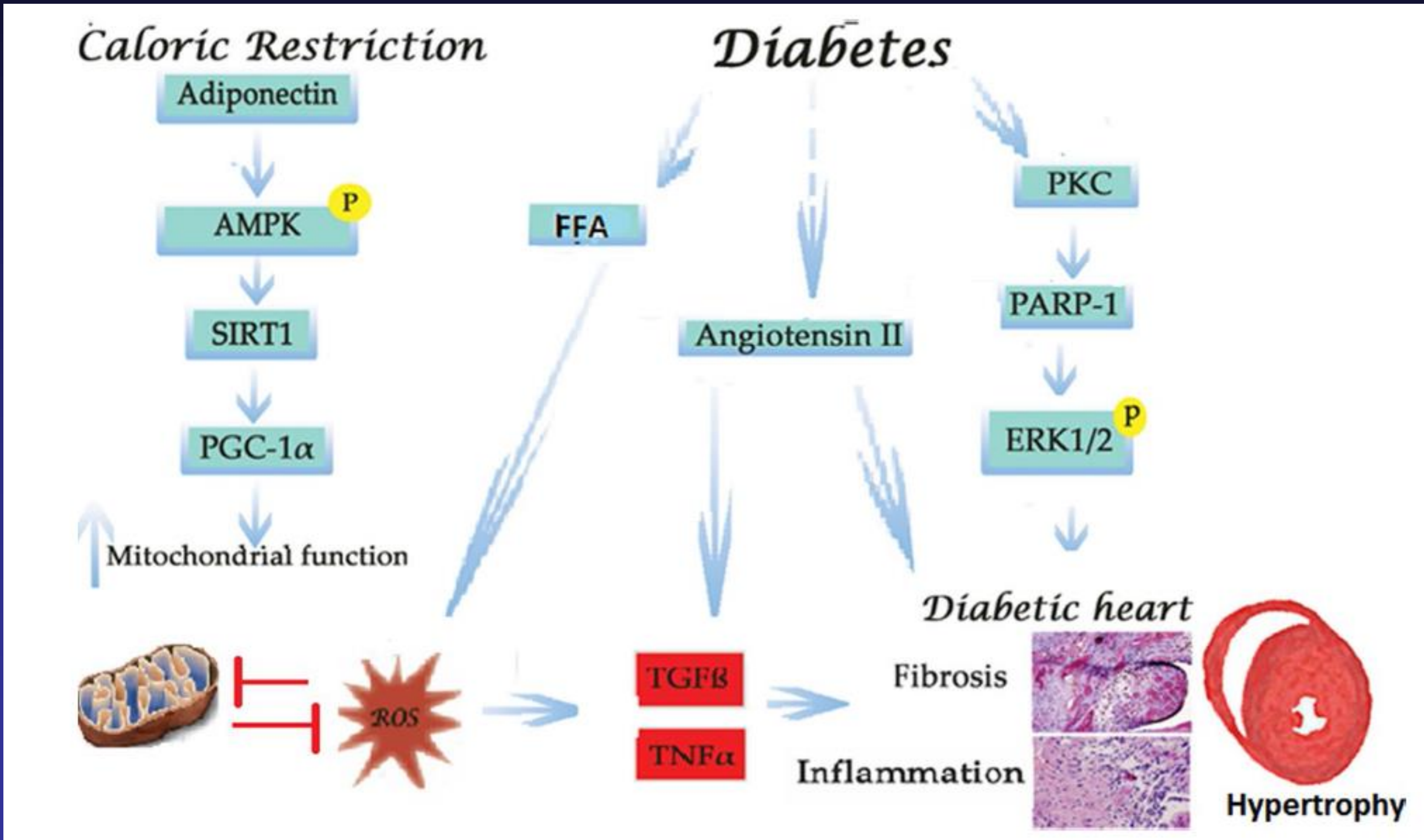
	WT n=7	WT+AT n=9	db/db n=11	db/db+AT n=14	db/db+AT+CR n=8
FS (%)	33±14	21±7*	34±7	30 ±7	41±10$^{\&}$
LVPW(d) (mm)	0.9±0.1	1±0.1	0.9±0.1	1.1±0.2$^{\#}$	0.9±0.2$^{\&}$
LVPW(s) (mm)	1.2±0.1	1.1±0.1	1.2±0.2	1.5±0.3$^{\#}$	1.2±0.3$^{\&}$
IVS(d) (mm)	0.8±0.1	0.9±0.1	0.9±0.1	1.1±0.1$^{\#}$	1±0.1$^{\&}$
LVEDD (mm)	3.6±0.7	4.2±0.4*	3.9±0.2	3.5±0.05$^{\#}$	4.1±0.4$^{\&}$

*p<0.05 vs. WT , $^{\#}$p<0.05 vs. db/db, $^{\&}$p<0.05 vs. db/db+AT

Cohen K, et al., Experimental Cell Research 2017

Caloric restriction attenuates cardiomyopathy in diabetic mice through the activation of 'SIRT1 - PGC-1α - HO-1' axis

Waldman M et al, Cardiovasc Diabetol 2018



Experimental design

db/db males
Age 14 weeks

Angiotensin infusion or Saline through osmotic pump

day 0 — 30

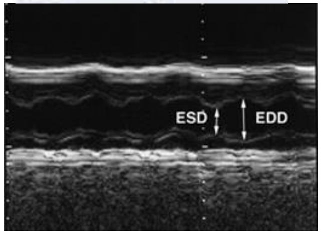
Normal tap water

Dapagliflozin 1.5 mg/kg/day in drinking water

In vivo

→

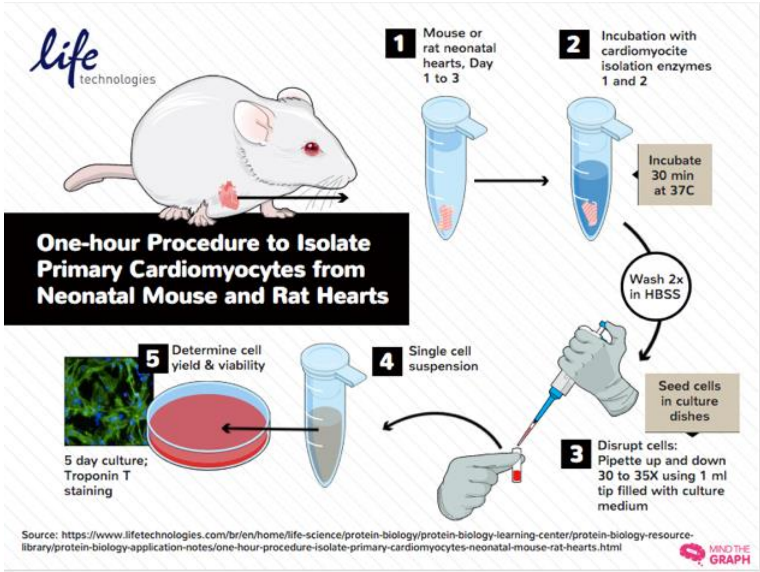
Blood pressure



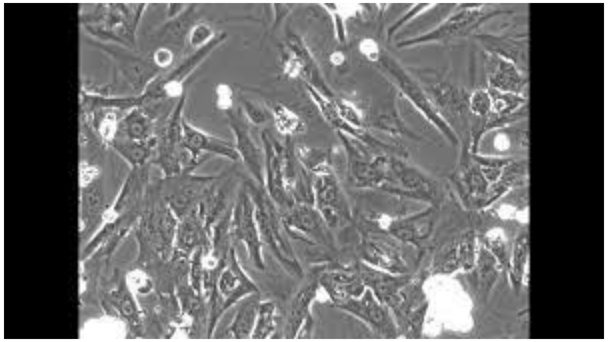
Echocardiography

Blood and tissue collection

In vitro



Normal rat neonatal cardiomyocytes
Normal or high glucose in medium
Dapagliflozin or Saline



Dapagliflozin reduces serum glucose and blood pressure

Table 1: Body and heart weight and biochemical markers

Groups/mice	Wt/wt	Wt/wt +ATII	Db/db	Db/db +DAPA	Db/db +ATII	Db/db+ATII +DAPA
numbers	8	6	5	4	8	5
Body weight (g)	25.5±1	25.5±1.5	41.5±5^{+}	42.8±2^{+}	38.8±8^{+}	45.3±5^{+}
Blood pressure(mmHg)	95±5	137±5^{+}	102±3	97±3	147±3$^{+,*}$	133±2$^{+,*,\#}$
Blood glucose(mg/dl)	298±55	258±76	937±75^{+}	607±30$^{+,*}$	874±111^{+}	556±57$^{+,\&}$
Blood cholesterol	118±25	143±5	120±10	143±22	202±77	188±35

$^{+}$ P<0.05 vs. wt/*wt*, * P<0.05 vs. *db/db*, $^{\&}$ P<0.05 vs *db/db*+ATII, $^{\#}$ p<0.002 vs *db/db*+ATII

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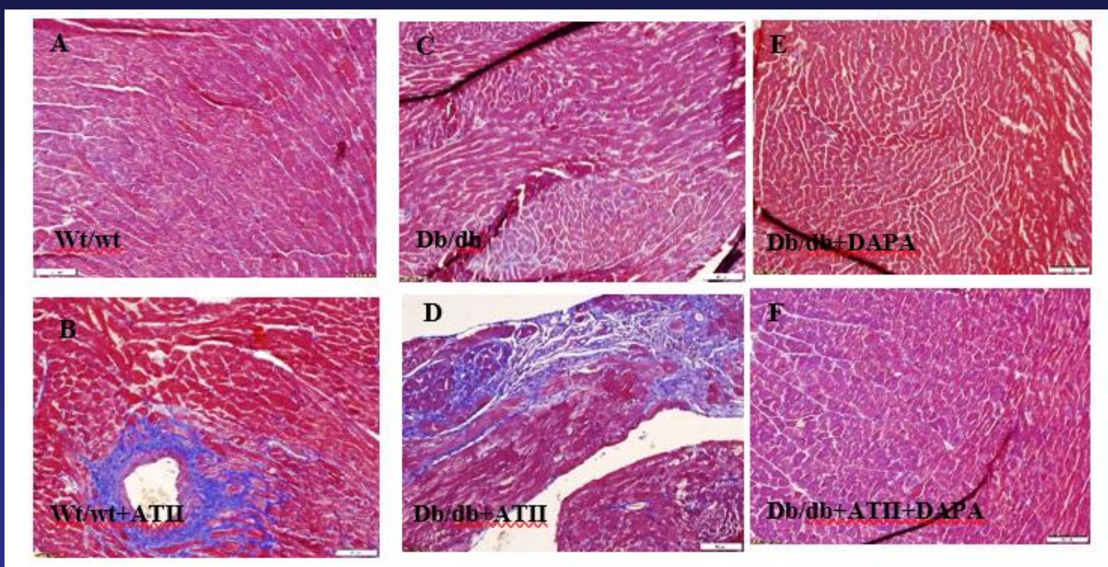
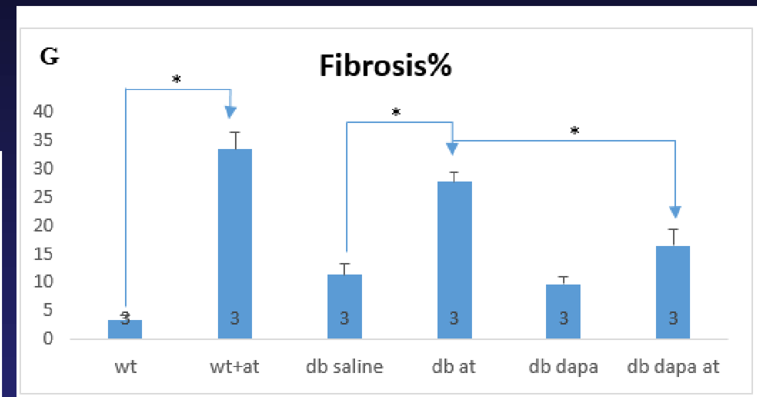
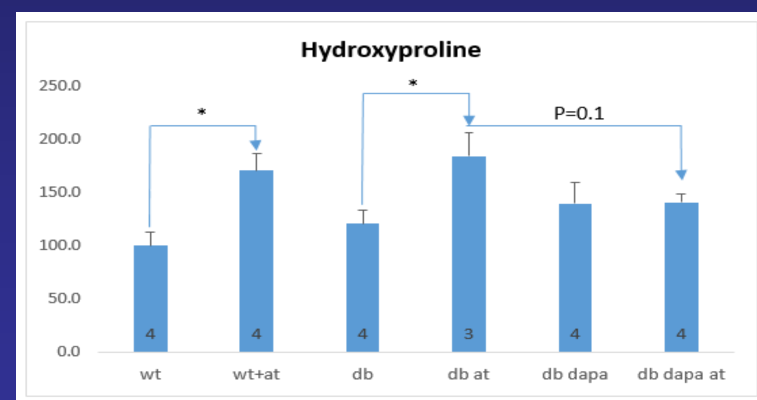
Dapagliflozin attenuates myocardial fibrosis in the diabetic heart

WT | DB | DB+Dapa

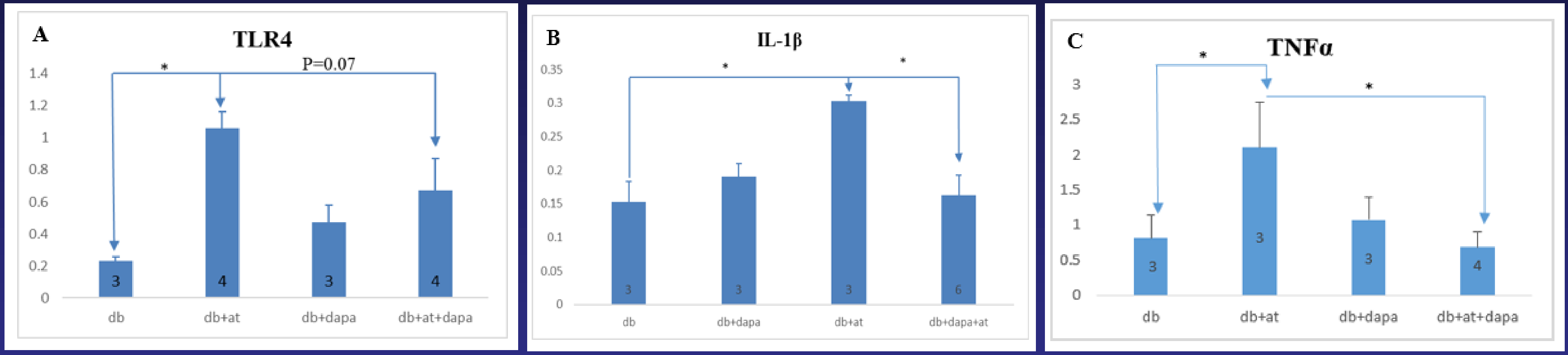


WT+ATII | DB+ATII | DB+ATII + Dapa

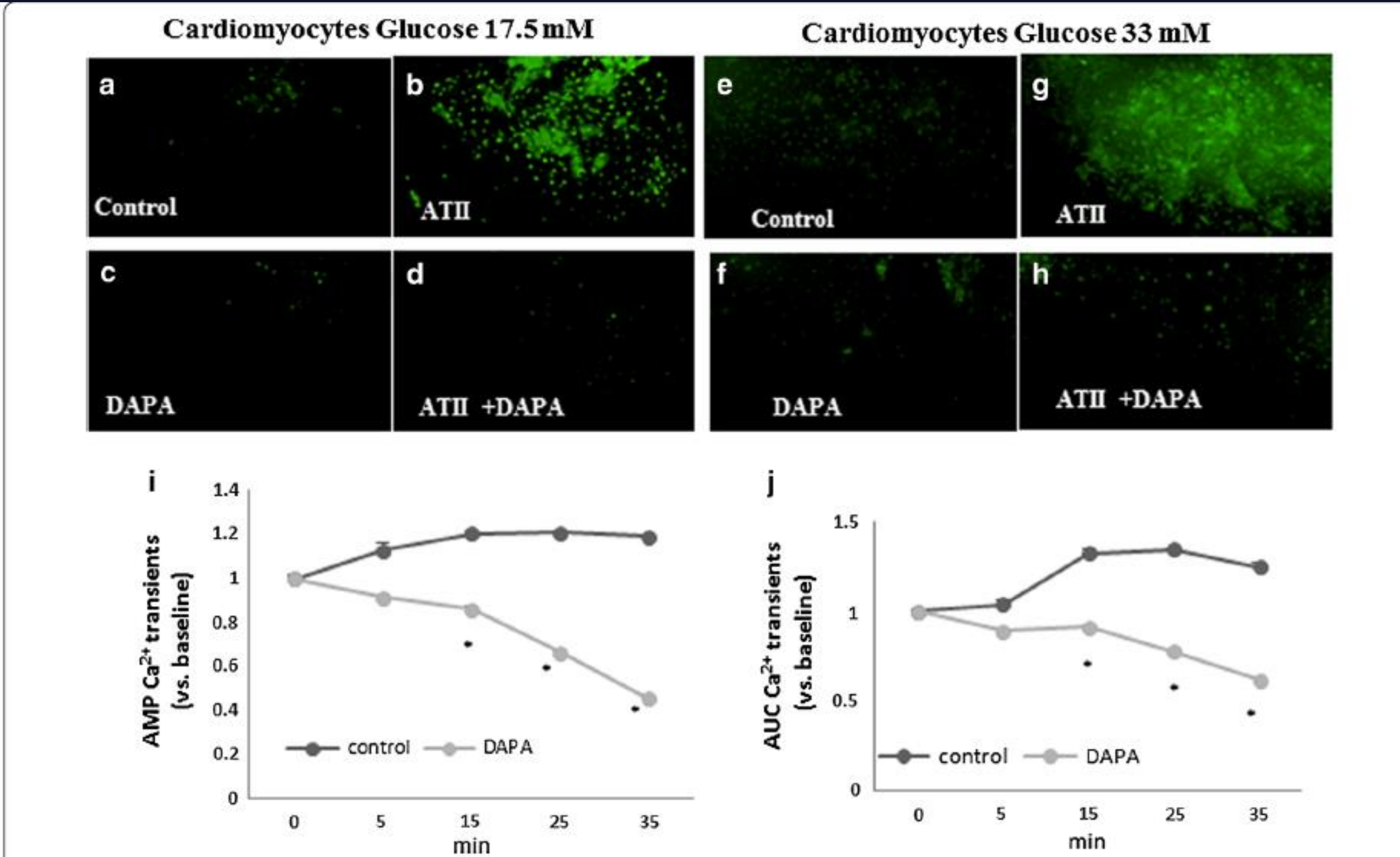




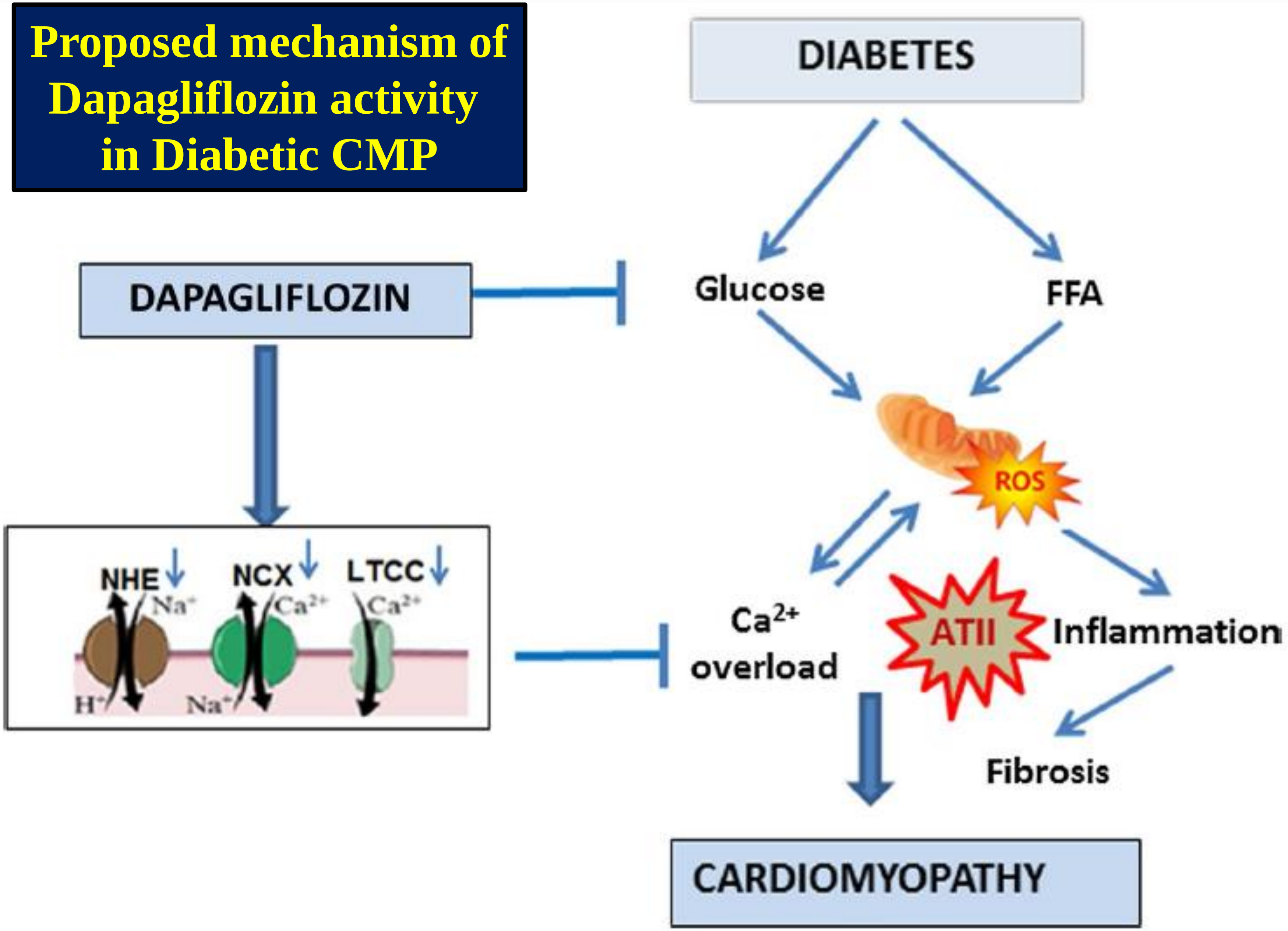
Dapagliflozin reduces the inflammation markers in the diabetic heart under angiotensin II stress



Dapaagliflozin reduces oxygen radical load and Ca^{+2} accumulation in cardiomyocytes



Proposed mechanism of Dapagliflozin activity in Diabetic CMP

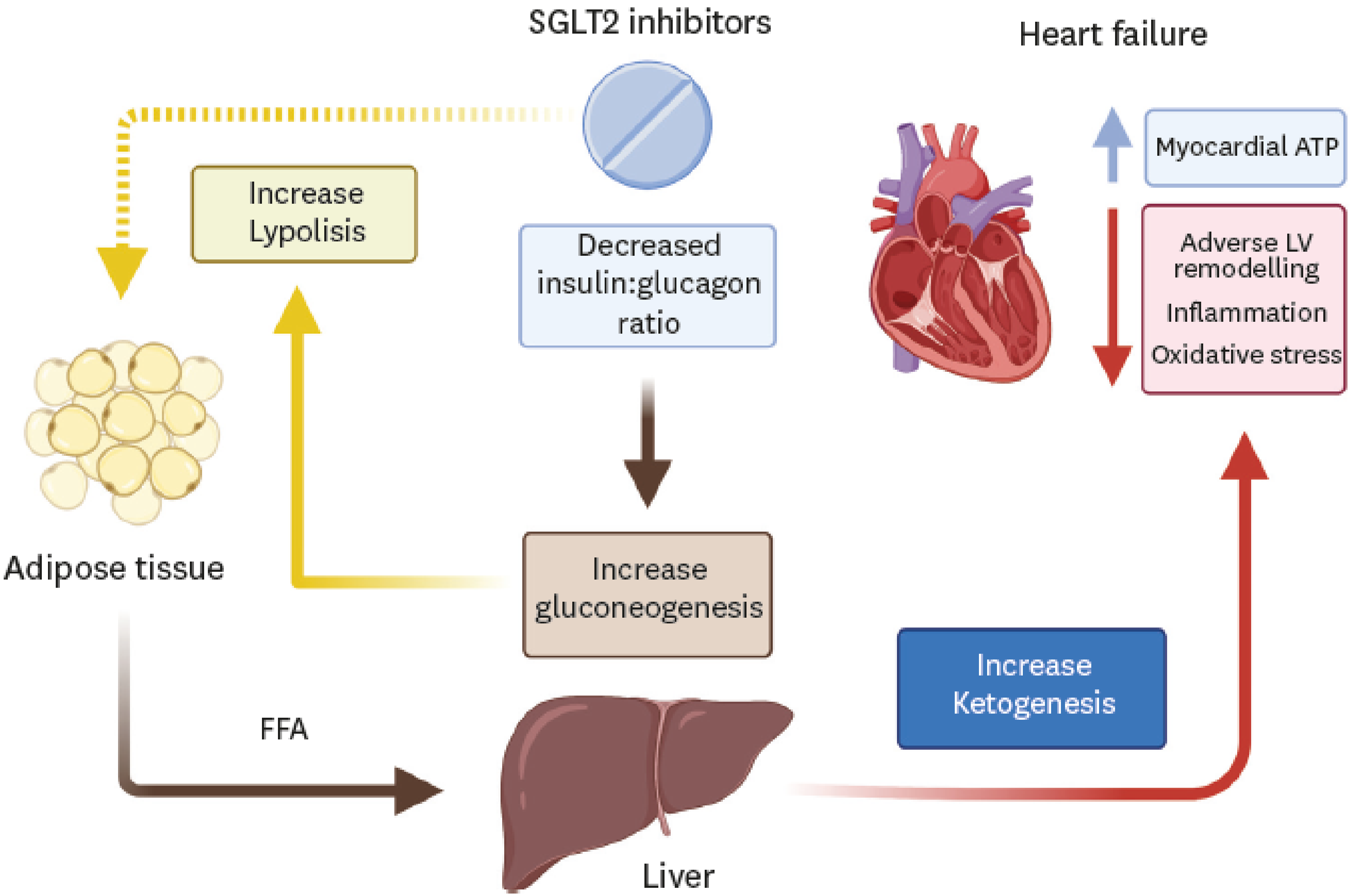


Arow M, et al., Cardiovascular Diabetol 2020

J Lipid Atheroscler. 2022 Jan;11(1):1-19
https://doi.org/10.12997/jla.2022.11.1.1
pISSN 2287-2892·eISSN 2288-2561

Journal of Lipid and Atherosclerosis

SGLT2i generate ketone bodies – good or bad?



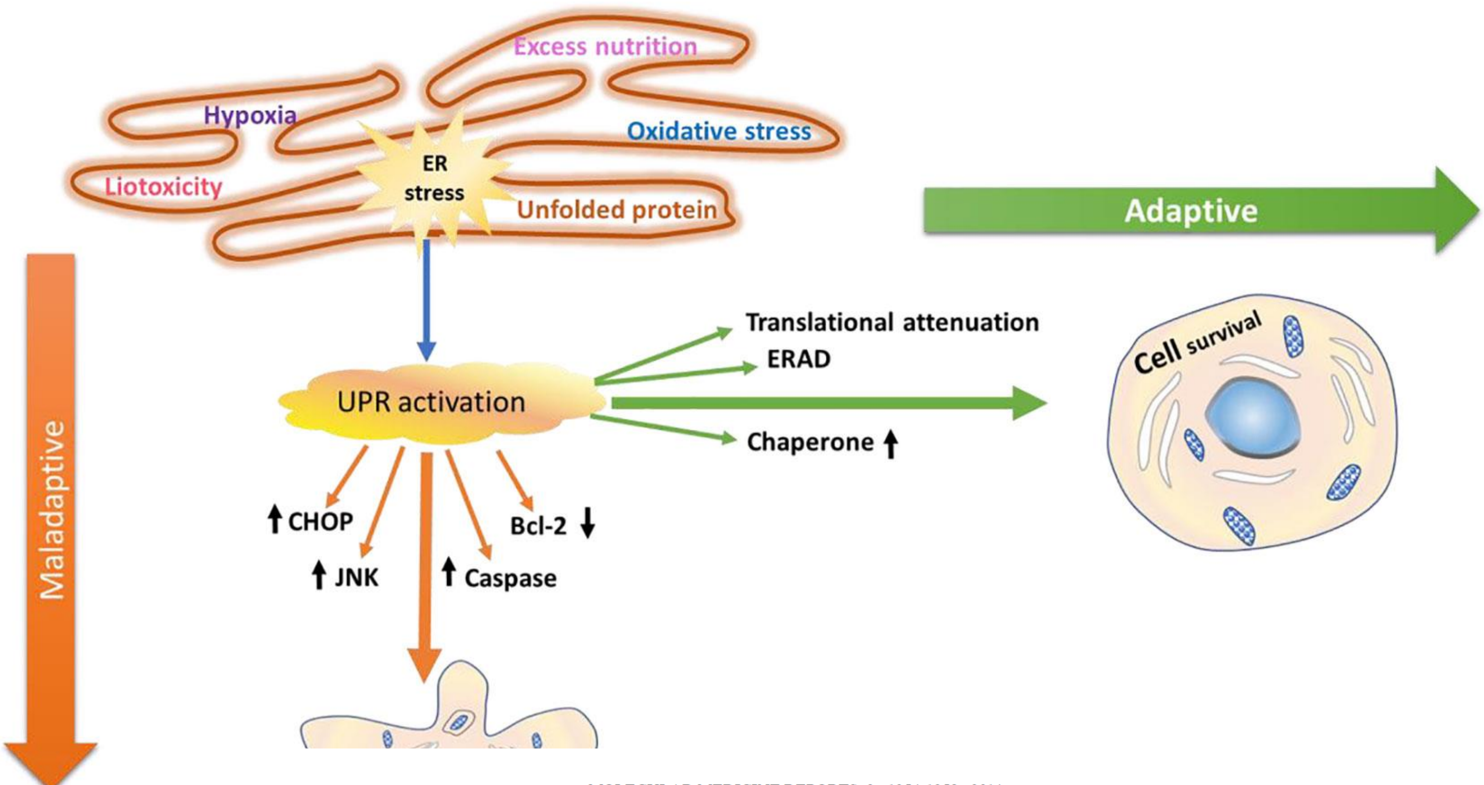
Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

SIRT1 suppresses cardiomyocyte apoptosis in diabetic cardiomyopathy: An insight into endoplasmic reticulum stress response mechanism☆

Rong Guo [a,b,*], Weijing Liu [a], Baoxin Liu [a], Buchun Zhang [c], Weiming Li [a], Yawei Xu [a,*]



MOLECULAR MEDICINE REPORTS 9: 1254-1258, 2014

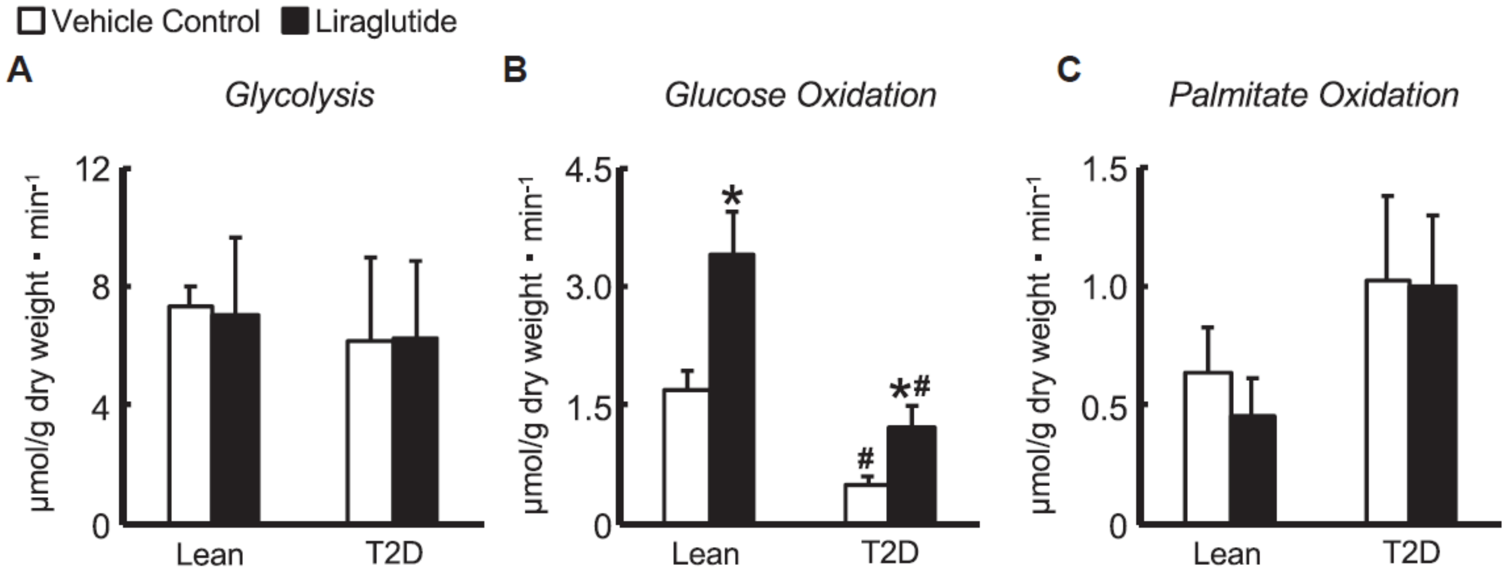
n N-terminal
egradation (ERAD)

Liraglutide alleviates diabetic cardiomyopathy by blocking CHOP-triggered apoptosis via the inhibition of the IRE-α pathway

YUQIANG JI[1], ZHAO ZHAO[1], TIANZHI CAI[2], PENGKANG YANG[1] and MANLI CHENG[1]

The GLP-1 Receptor Agonist Liraglutide Increases Myocardial Glucose Oxidation Rates via Indirect Mechanisms and Mitigates Experimental Diabetic Cardiomyopathy

Almutairi et al, Can J Cardiol 2021



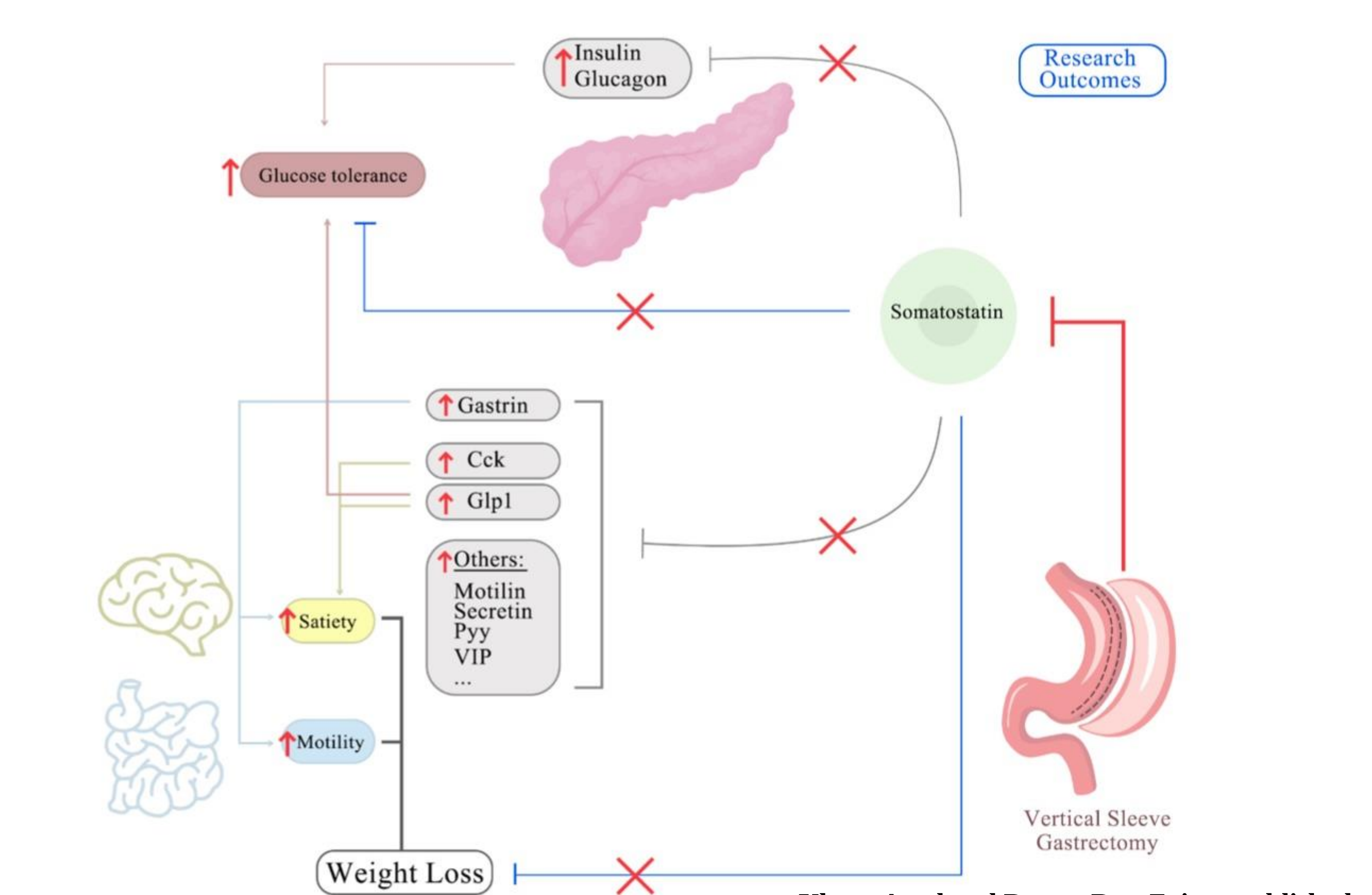
GLP-1 analog liraglutide-induced cardiac dysfunction due to energetic starvation in heart failure with non-diabetic dilated cardiomyopathy **Cardiovasc Diabetol 2019**

Aya Shiraki, Jun-ichi Oyama*, Toshiyuki Nishikido and Koichi Node

N HF HF-L HF-H

J2N-n (normal) J2N-k (heart failure)

Effects of bariatric surgery in mice, GLP1 and the postulated role of somatostatin



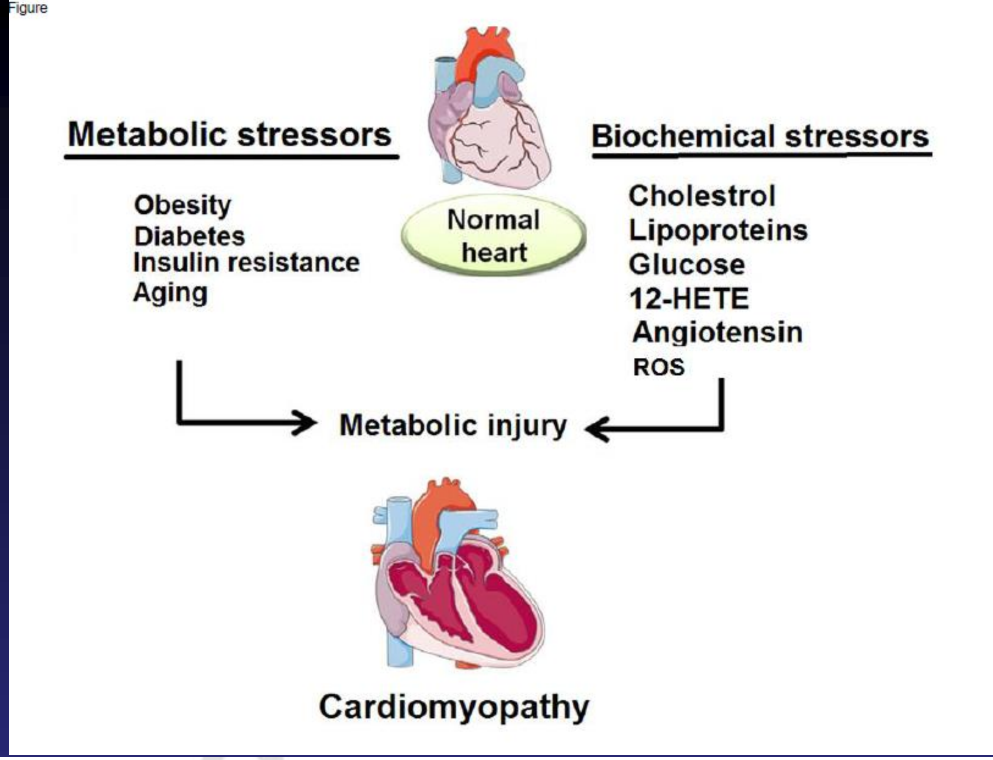
Yhara Arad and Danny Ben-Zvi, unpublished

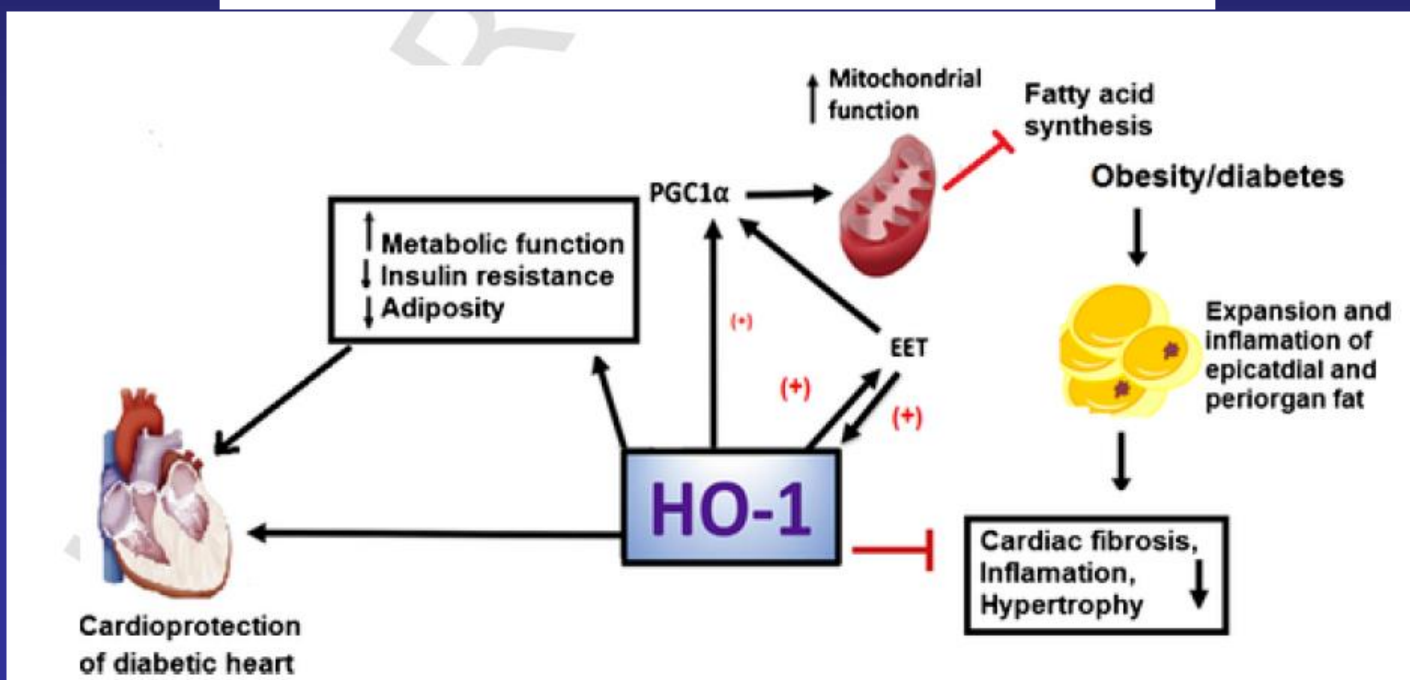
Thank you and my dear students and collaborators !

- **Keren Cohen M.Sc**
- **Mais Arow M. Sc**
- **Dor Yadin M. Sc (soon Ph.D)**
- **Maayan Waldman Ph.D**
- **Yishai Wasserstrum MD**
- **Prof. Edith Hochhauser**
- **Prof. Nader Abraham**
- **Prof. Dov Freimark**

Arad et al, 2020

Prostaglandins and other lipids





Dapagliflozin improves systolic function in the diabetic heart under stress

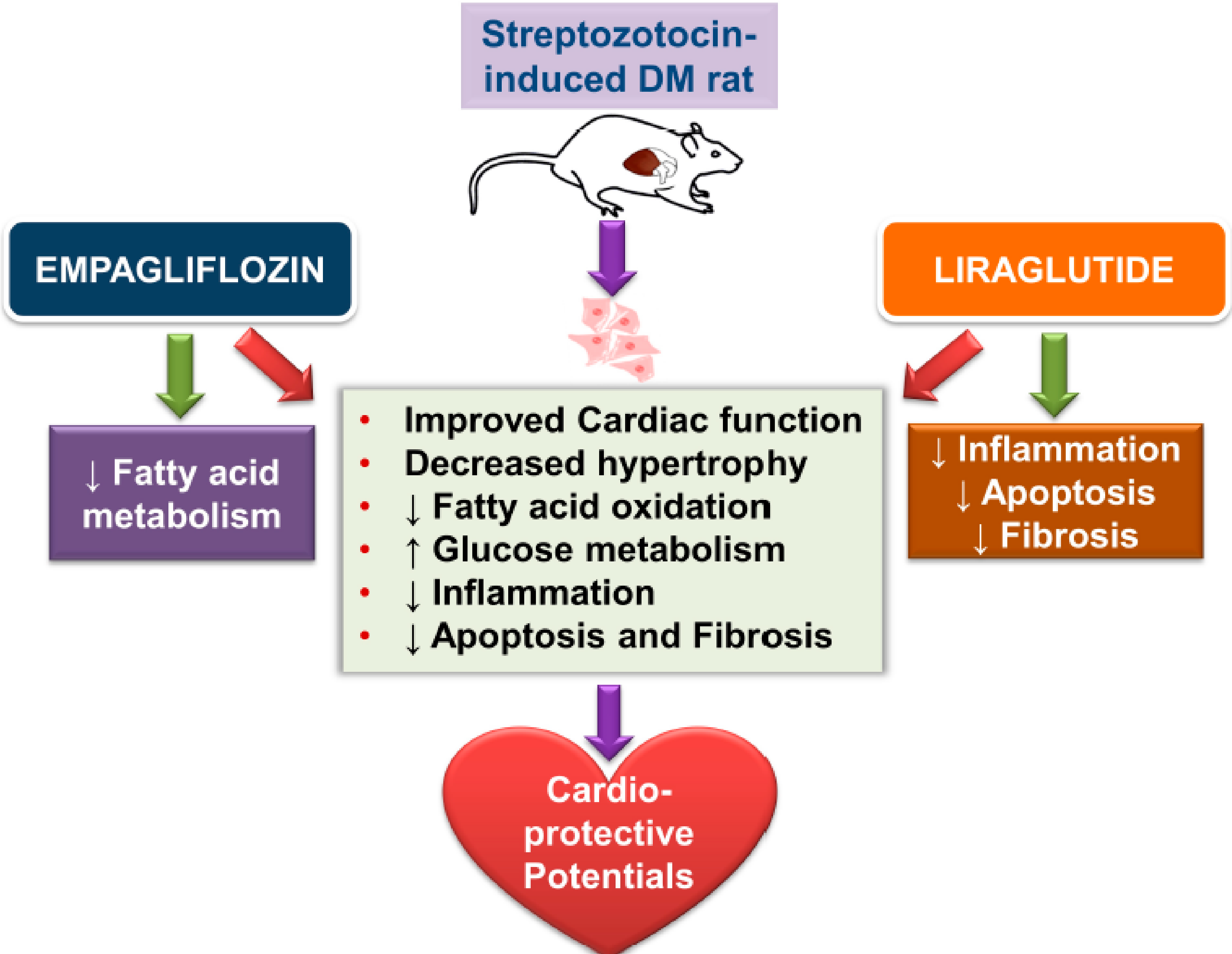
Table 2:Heart dimensions and function

	Wt/wt	Wt/wt +ATII	Db/db	Db/db +DAPA	Db/db +ATII	Db/db+ATII +DAPA
numbers	6	6	5	4	6	6
IVS	0.9±0.1	1.2±0.08[&]	0.96±0.08	0.97±0.1	1.2±0.1[#]	1.2±0.2
LVPW	0.8±0.05	1.1±0.12[&]	0.9±0.1	0.9±0.3	1.1±0.1[#]	1.2±0.3
LVEDD	3.8±0.2	3.4±0.3	3.5±0.5	3.7±0.6	3.7±0.4	3.4±0.6
LVESD	2.4±0.1	2.3±0.3	2.1±0.5	2.2±0.5	2.4±0.3	1.9±0.5[*]
FS	36.2±2.2	31.9±4.9	39.4±6.2	39.7±6.3	34.9±2.6	45.9±6.5[*]

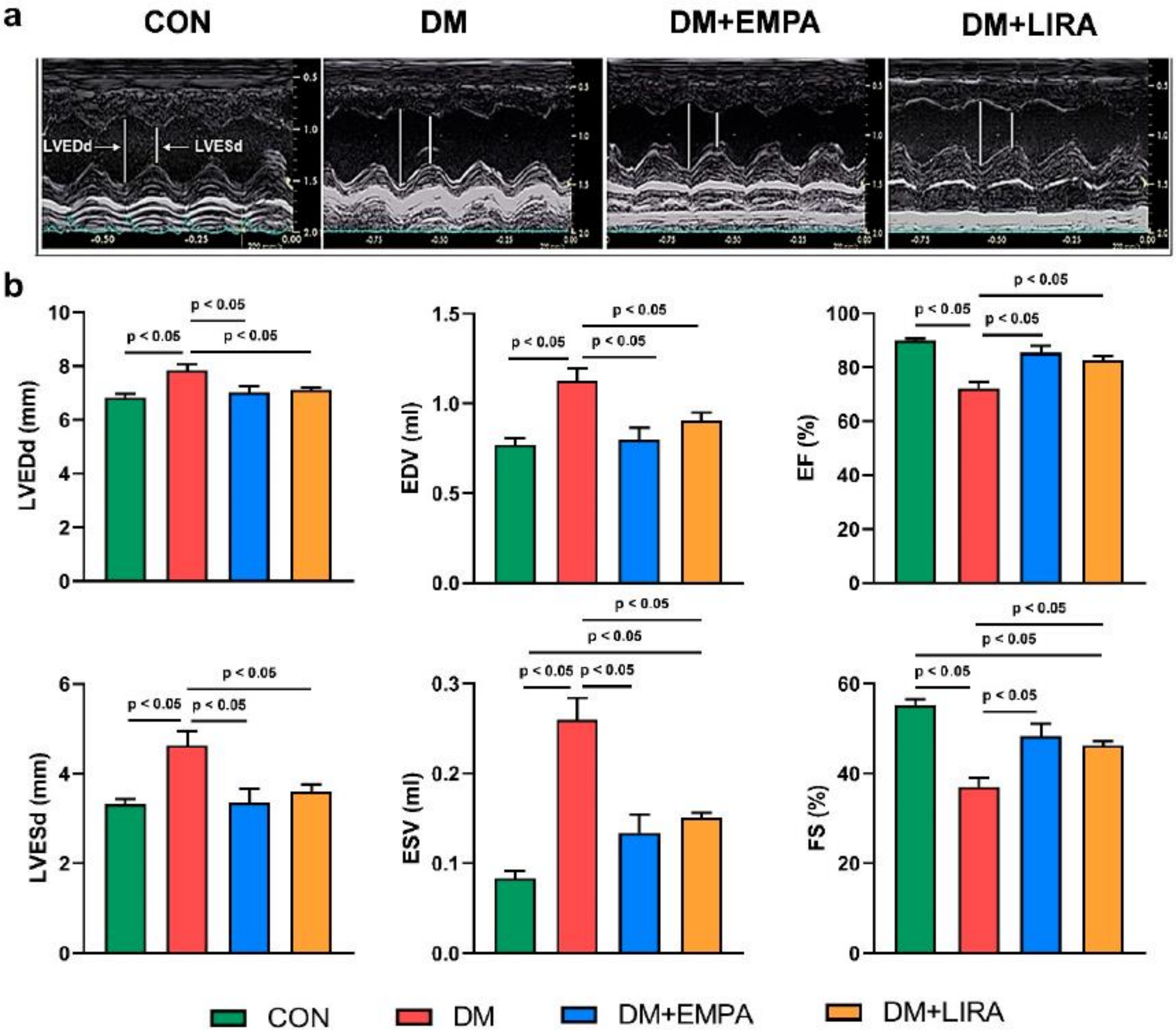
* P<0.05 vs *db/db*+ATII, # P<0.05 vs. *db/db*, & P<0.05 vs. wt/wt

Empagliflozin and Liraglutide Differentially Modulate Cardiac Metabolism in Diabetic Cardiomyopathy in Rats

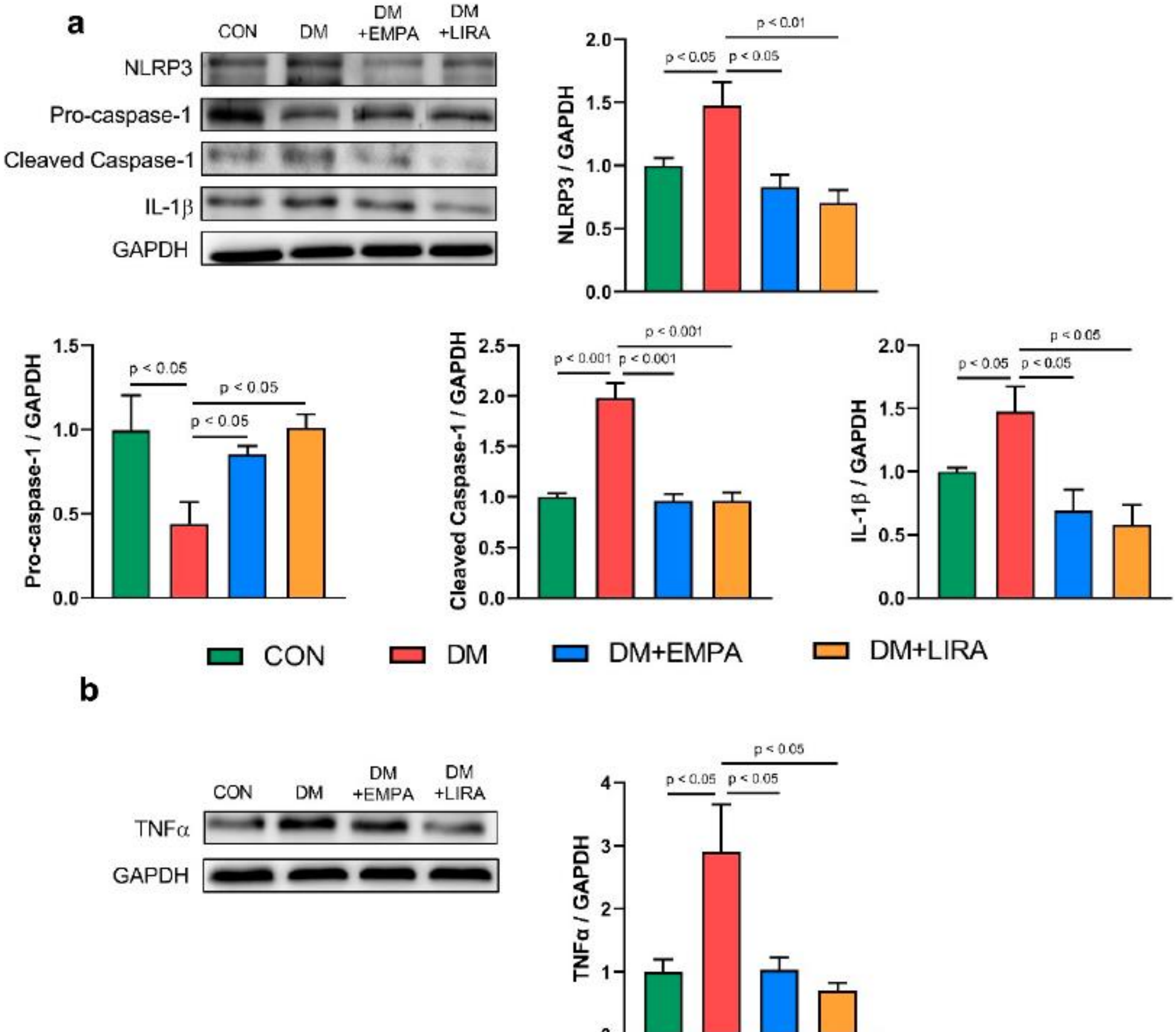
Nguyen Ngoc Trang [1], Cheng-Chih Chung [2,3], Ting-Wei Lee [4,5], Wan-Li Cheng [2,6], Yu-Hsun Kao [2,6], Shih-Yu Huang [7], Ting-I Lee [4,5,8,*] and Yi-Jen Chen [2,3,6]



Int. J Med Sciences 2021



a
CON
DM
DM+EMPA
DM+LIRA
LVEDd
LVESd
b
LVEDd (mm)
EDV (ml)
EF (%)
LVESd (mm)
ESV (ml)
FS (%)
p < 0.05
CON
DM
DM+EMPA
DM+LIRA


a
CON
DM
DM +EMPA
DM +LIRA
NLRP3
Pro-caspase-1
Cleaved Caspase-1
IL-1β
GAPDH
NLRP3 / GAPDH
p < 0.05
p < 0.05
p < 0.01
Pro-caspase-1 / GAPDH
p < 0.05
p < 0.05
p < 0.05
Cleaved Caspase-1 / GAPDH
p < 0.001
p < 0.001
p < 0.001
IL-1β / GAPDH
p < 0.05
p < 0.05
p < 0.05
CON
DM
DM+EMPA
DM+LIRA
b
CON
DM
DM +EMPA
DM +LIRA
TNFα
GAPDH
TNFα / GAPDH
p < 0.05
p < 0.05
p < 0.05