OBESITY IN THE ELDERLY

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THE PATHOPHYSIOLOGICAL CHANGES THAT OCCUR WITH OBESITY ARE SIMILAR TO OR CONTRIBUTE TO THOSE THAT OCCUR WITH AGING.

OBESITY

Obesity-related dementia?

Cardiovascular:
- Coronary heart disease
- Vascular dysfunction
- SNS hyperactivation

Glomerulopathy

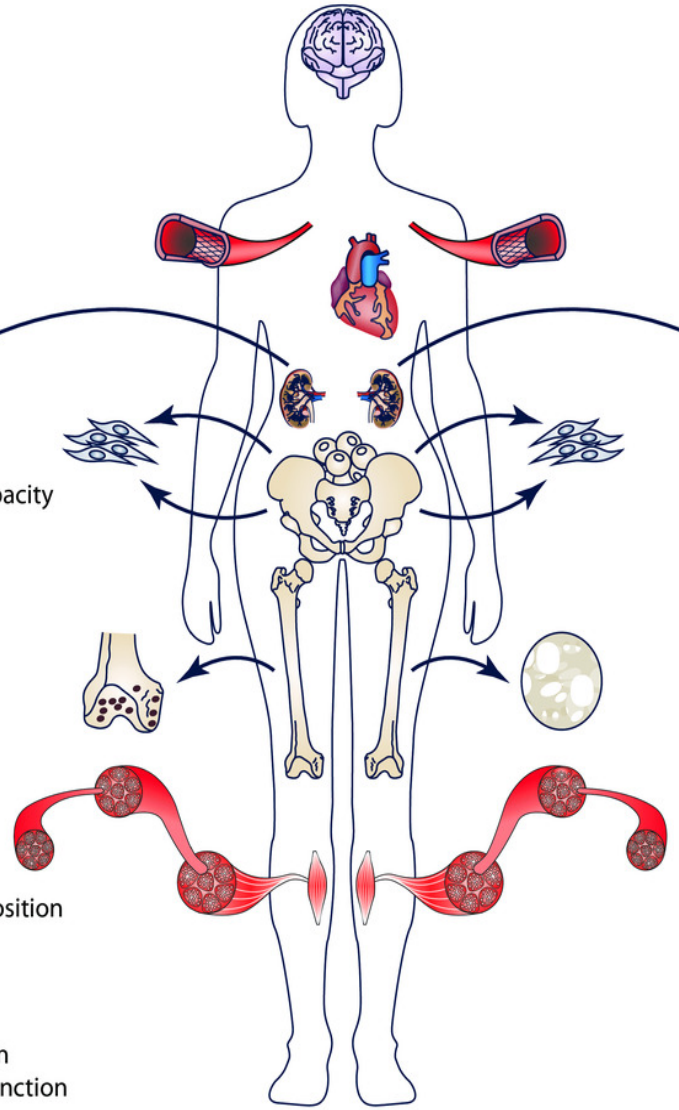
Stem cell population:
- Impaired regenerative capacity

Bone alteration:
- Increased fracture risk

Skeletal muscle:
- Metabolic alteration

Altered muscle fibre composition

Chronic inflammation
Altered immune system function



AGING

Ageing neurodegeneration:
- Cognitive decline
- Higher dementia risk

Cardiovascular ageing:
- Myocardium defects
- Vascular alteration
- SNS hyperactivation

Structural and renal changes

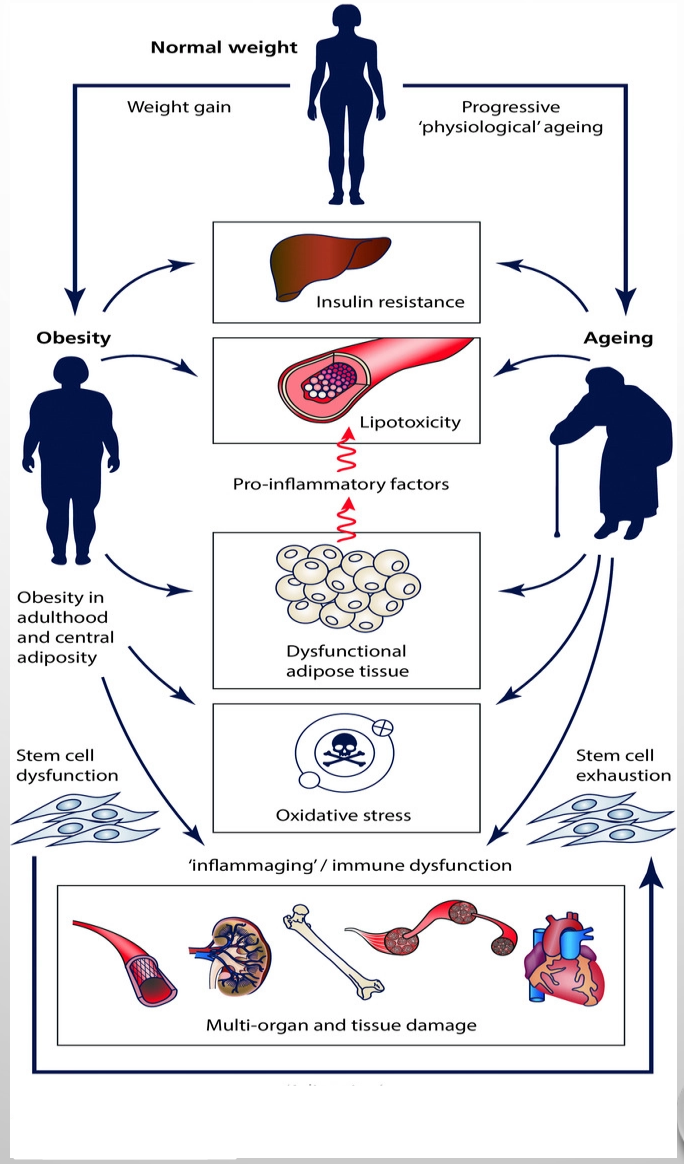
Stem cell population:
- Impaired regenerative capacity
- Stem cell exhaustion

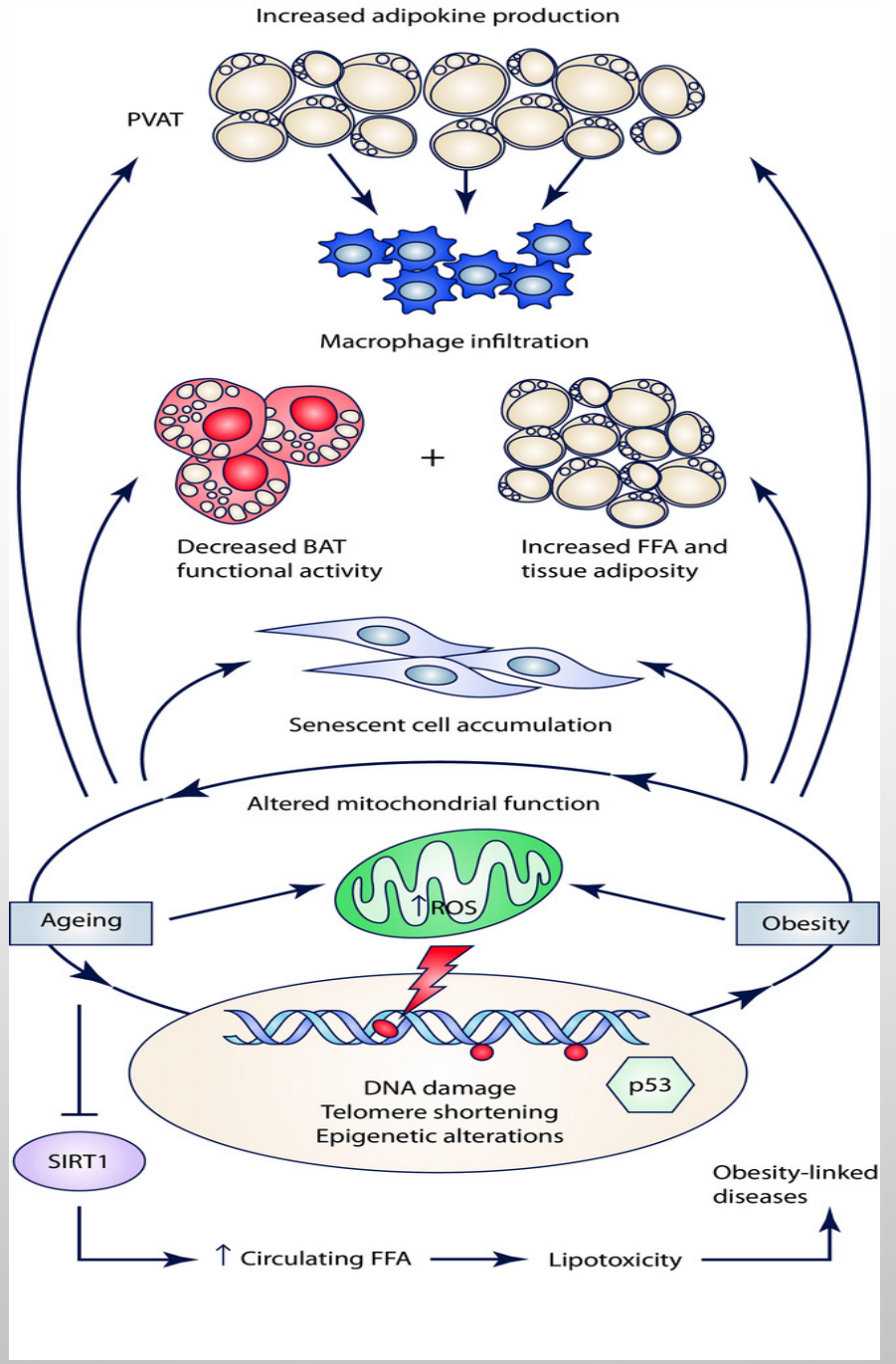
Bone loss:
- Increased fracture risk

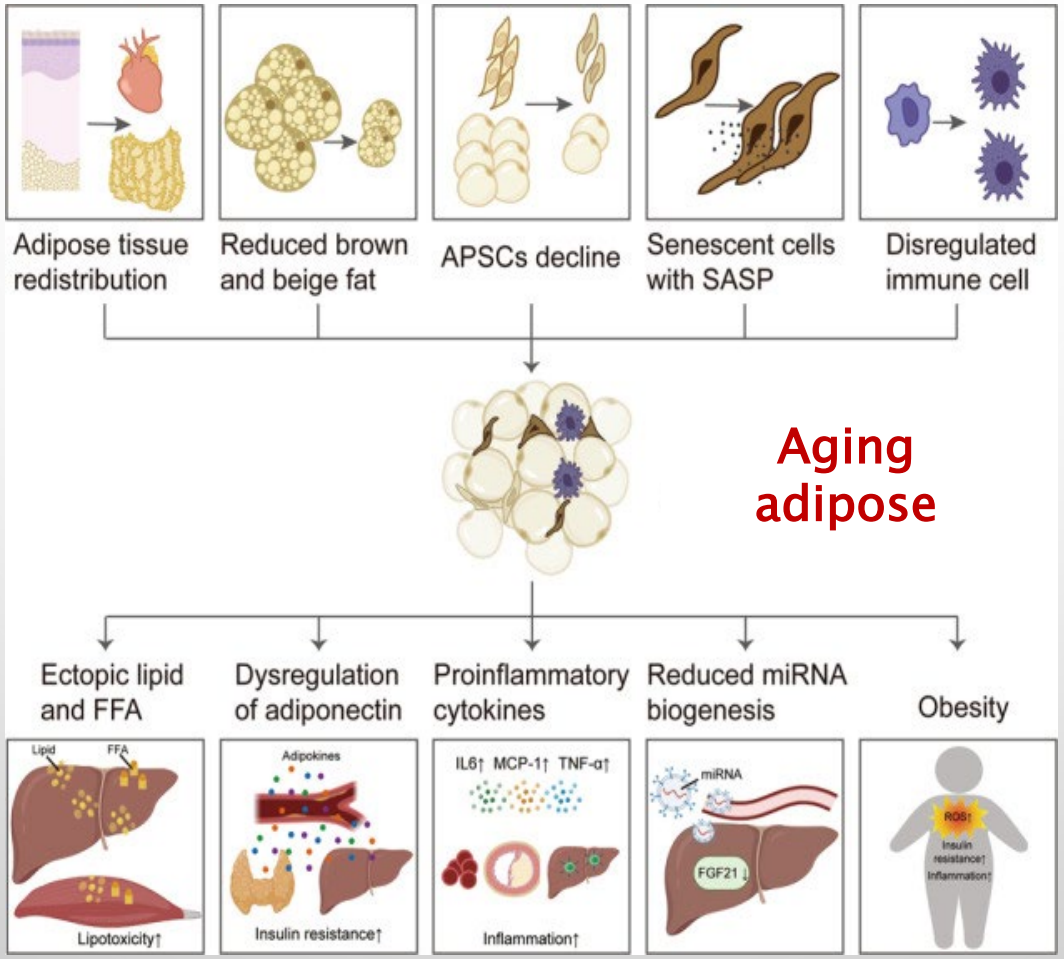
Skeletal muscle:
- Loss of muscle
- Muscle fibre replacement

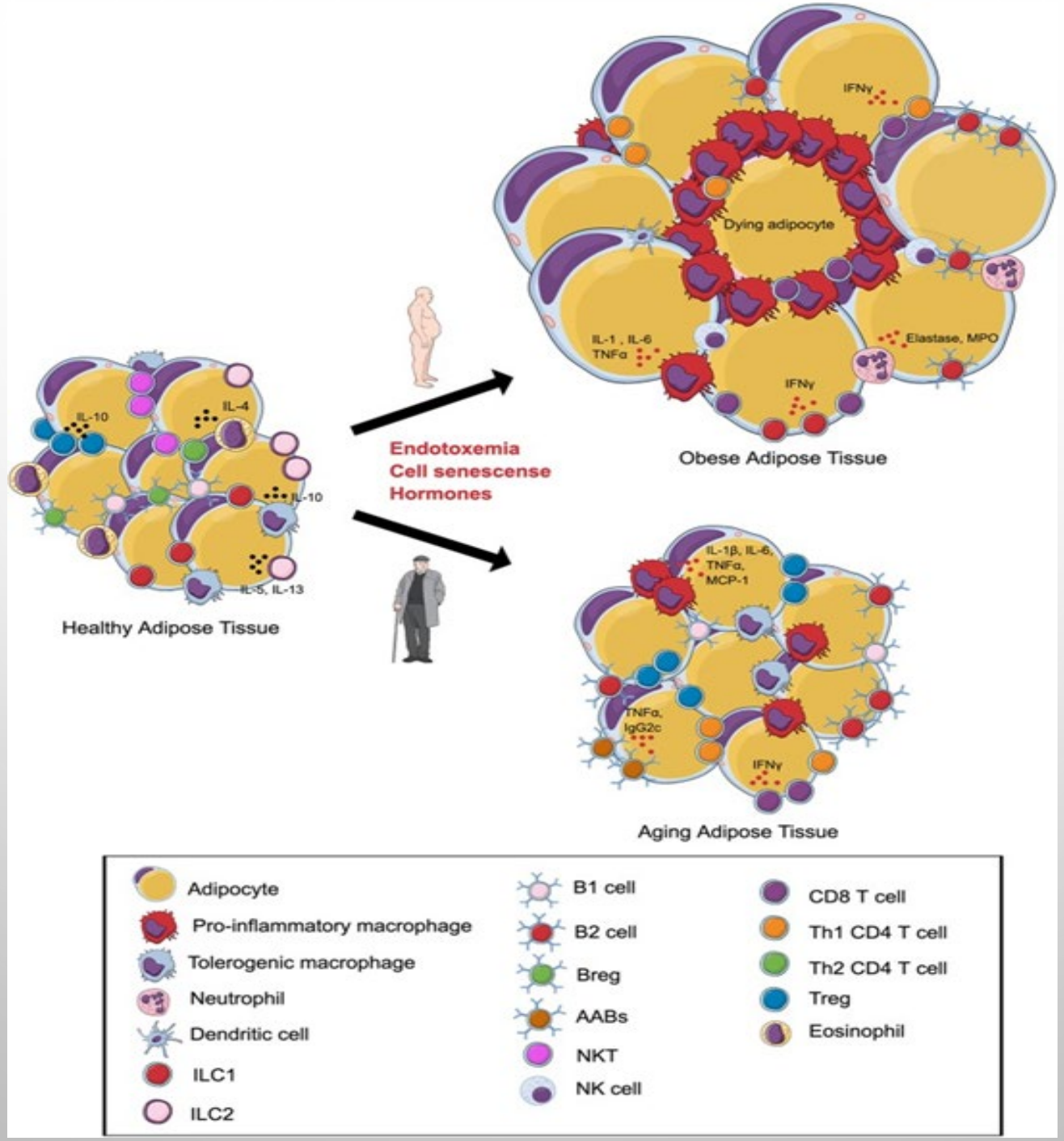
Inflammageing
Immune system senescence

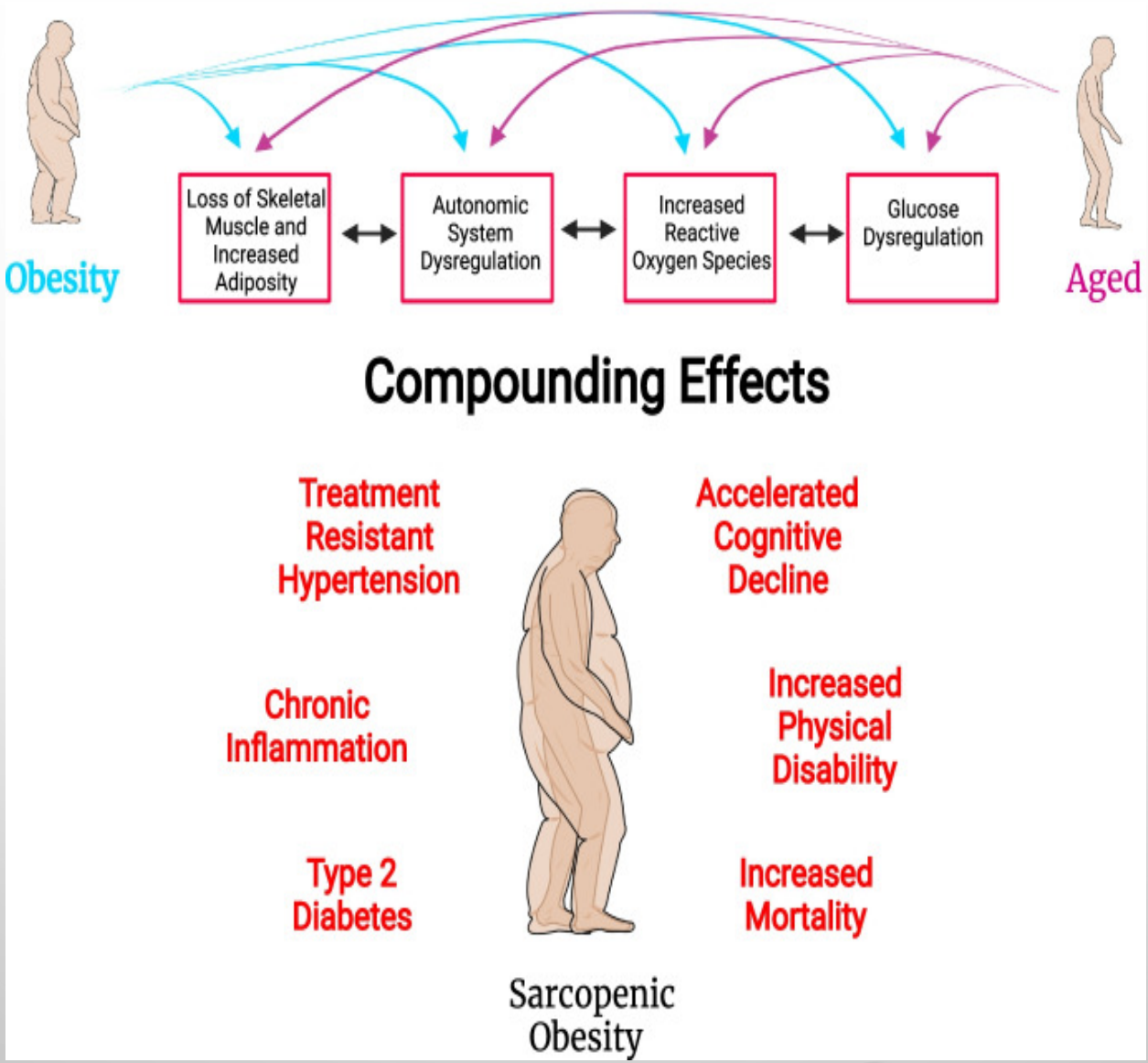
ADIPAGING


Normal weight
Weight gain
Progressive 'physiological' ageing
Insulin resistance
Obesity
Ageing
Lipotoxicity
Pro-inflammatory factors
Obesity in adulthood and central adiposity
Dysfunctional adipose tissue
Stem cell dysfunction
Oxidative stress
Stem cell exhaustion
'inflammaging' / immune dysfunction
Multi-organ and tissue damage


Increased adipokine production
PVAT
Macrophage infiltration
Decreased BAT
functional activity
+
Increased FFA and
tissue adiposity
Senescent cell accumulation
Altered mitochondrial function
↑ROS
Ageing
Obesity
DNA damage
Telomere shortening
Epigenetic alterations
p53
SIRT1
Obesity-linked
diseases
↑ Circulating FFA
Lipotoxicity


Adipose tissue redistribution
Reduced brown and beige fat
APSCs decline
Senescent cells with SASP
Disregulated immune cell
Aging adipose
Ectopic lipid and FFA
Dysregulation of adiponectin
Proinflammatory cytokines
Reduced miRNA biogenesis
Obesity
Lipid
FFA
Lipotoxicity↑
Adipokines
Insulin resistance↑
IL6↑ MCP-1↑ TNF-α↑
Inflammation↑
miRNA
FGF21↓
ROS↑
Insulin resistance↑
Inflammation↑


IFNγ
Dying adipocyte
IL-1 , IL-6
TNFα
Elastase, MPO
IFNγ
Obese Adipose Tissue
IL-10
IL-4
IL-10
IL-5, IL-13
Healthy Adipose Tissue
Endotoxemia
Cell senescense
Hormones
IL-1β, IL-6,
TNFα,
MCP-1
TNFα,
IgG2c
IFNγ
Aging Adipose Tissue
Adipocyte
Pro-inflammatory macrophage
Tolerogenic macrophage
Neutrophil
Dendritic cell
ILC1
ILC2
B1 cell
B2 cell
Breg
AABs
NKT
NK cell
CD8 T cell
Th1 CD4 T cell
Th2 CD4 T cell
Treg
Eosinophil

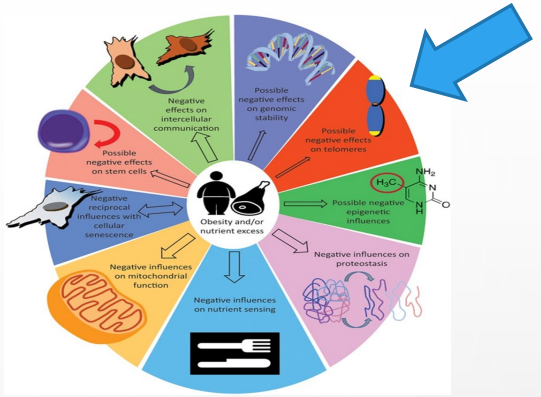

Obesity
Loss of Skeletal Muscle and Increased Adiposity
Autonomic System Dysregulation
Increased Reactive Oxygen Species
Glucose Dysregulation
Aged
Compounding Effects
Treatment Resistant Hypertension
Accelerated Cognitive Decline
Chronic Inflammation
Increased Physical Disability
Type 2 Diabetes
Increased Mortality
Sarcopenic Obesity

OBESITY MAY ACCELERATE THE AGING PROCESS

NINE HALLMARKS DEFINE THE AGING PROCESS:

- TELOMERE ATTRITION
- EPIGENETIC ALTERATION
- MITOCHONDRIAL DYSFUNCTION
- CELLULARE SENESCENCE
- STEM CELL EXHAUSTION
- DEREGULATED NUTRIENT SENSING
- ALTERED INTERCELLULAR COMMUNICATION
- GENOMIC INSTABILITY
- LOSS OF PROTEOSTASIS


Negative effects on intercellular communication
Possible negative effects on genomic stability
Possible negative effects on telomeres
Possible negative epigenetic influences
Negative influences on proteostasis
Negative influences on nutrient sensing
Negative influences on mitochondrial function
Negative reciprocal influences with cellular senescence
Possible negative effects on stem cells
Obesity and/or nutrient excess
NH2
H3C
N
N
H
O



ON THE POSSIBLE **LINKS BETWEEN OBESITY, TELOMERES AND AGING** IT IS MORE PRUDENT TO CONCLUDE THAT THE AVAILABLE STUDIES ARE HETEROGENEOUS AND SHOW A WEAK STATISTICAL SIGNIFICANCE.

SEVERAL REPORTS DEMONSTRATE THAT **NUTRITION AND OBESITY** ARE ABLE TO MODULATE THE EPIGENETIC SIGNATURE OF AN INDIVIDUAL, EVEN DURING PRENATAL DEVELOPMENT.

THE OBSERVED ALTERATIONS DO NOT ALWAYS OVERLAP THOSE SEEN IN AGING, HOWEVER SOME STUDIES SHOW A CLOSE CORRELATION BETWEEN EPIGENETIC ALTERATION INDUCED BY OBESITY AND AN ACCELERATION OF TISSUE AGING.

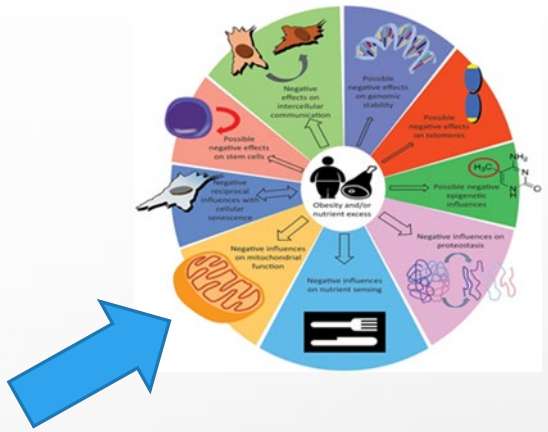
THIS SUGGESTS THAT OBESITY COULD ACCELERATE AGE-RELATED DYSFUNCTION BY INDUCING EPIGENETIC ALTERATIONS THAT ARE NOT NECESSARILY THE SAME AS THOSE OBSERVED DURING AGING IN NON-OBESE INDIVIDUALS.

IN BIOGERONTOLOGY, THE **INSULIN/INSULIN-LIKE GROWTH FACTOR (IGF-1) SIGNALING PATHWAY AND MTOR PATHWAY** ARE CONSIDERED "ACCELERATORS" OF THE AGING PROCESS, AND ARE OVER-ACTIVATED IN OBESITY.

IN CONTRAST, PRO LONGEVITY PATHWAYS, SUCH AS THE **AMPK AND SIRTUINS PATHWAYS** ARE DAMPENED BY OBESITY.

IN CONCLUSION, THERE IS SOLID EVIDENCE THAT OBESITY DEREGULATES CELLULAR MECHANISMS RELATED TO NUTRIENT SENSING.

- IN MICE NUTRIENT DEPLETION OR LONG-TERM **CALORIC RESTRICTION INCREASE SIRTUINS ACTIVITY** (IN PARTICULAR SIRTUIN-6) IN THE BRAIN, WHITE ADIPOSE TISSUE, MUSCLE, LIVER AND KIDNEY.



MITOCHONDRIAL DYSFUNCTION OCCURS IN AGED TISSUES, IN RESPONSE TO EXCESSIVE NUTRIENT INTAKE, AND IN OBESITY, CONTRIBUTING TO INFLAMMATION AND INSULIN RESISTANCE.

AGING AND OBESITY APPEAR SUPERIMPOSABLE IN THEIR IMPACT ON MITOCHONDRIA AND IT IS REASONABLE TO HYPOTHESIZE THAT THEY COULD EXERT ADDITIVE EFFECTS.

THERE APPEARS TO BE A STRONG RELATIONSHIP BETWEEN **OBESITY AND SENESCENCE.** OBESITY MAY PROMOTE THE AGING PROCESS BY INDUCING SENESCENCE.

CONVERSELY, SENESCENCE AND THE RESULTING PRO-INFLAMMATORY SECRETORY PHENOTYPE COULD CONTRIBUTE TO THE MORBIDITY ASSOCIATED WITH OBESITY AND PLAYS A ROLE IN THE DEVELOPMENT OF INSULIN RESISTANCE AND DIABETES.

FINALLY, **CALORIC RESTRICTION MIGHT EXERT ITS ANTI-AGING CAPACITIES BY LIMITING SENESCENT CELL ACCUMULATION.**

BOTH **OBESITY AND AGING**, NEGATIVELY IMPACT ADIPOSE-DERIVED **STEM CELLS**, NEURAL STEM CELLS AND BM HOMEOSTASIS.

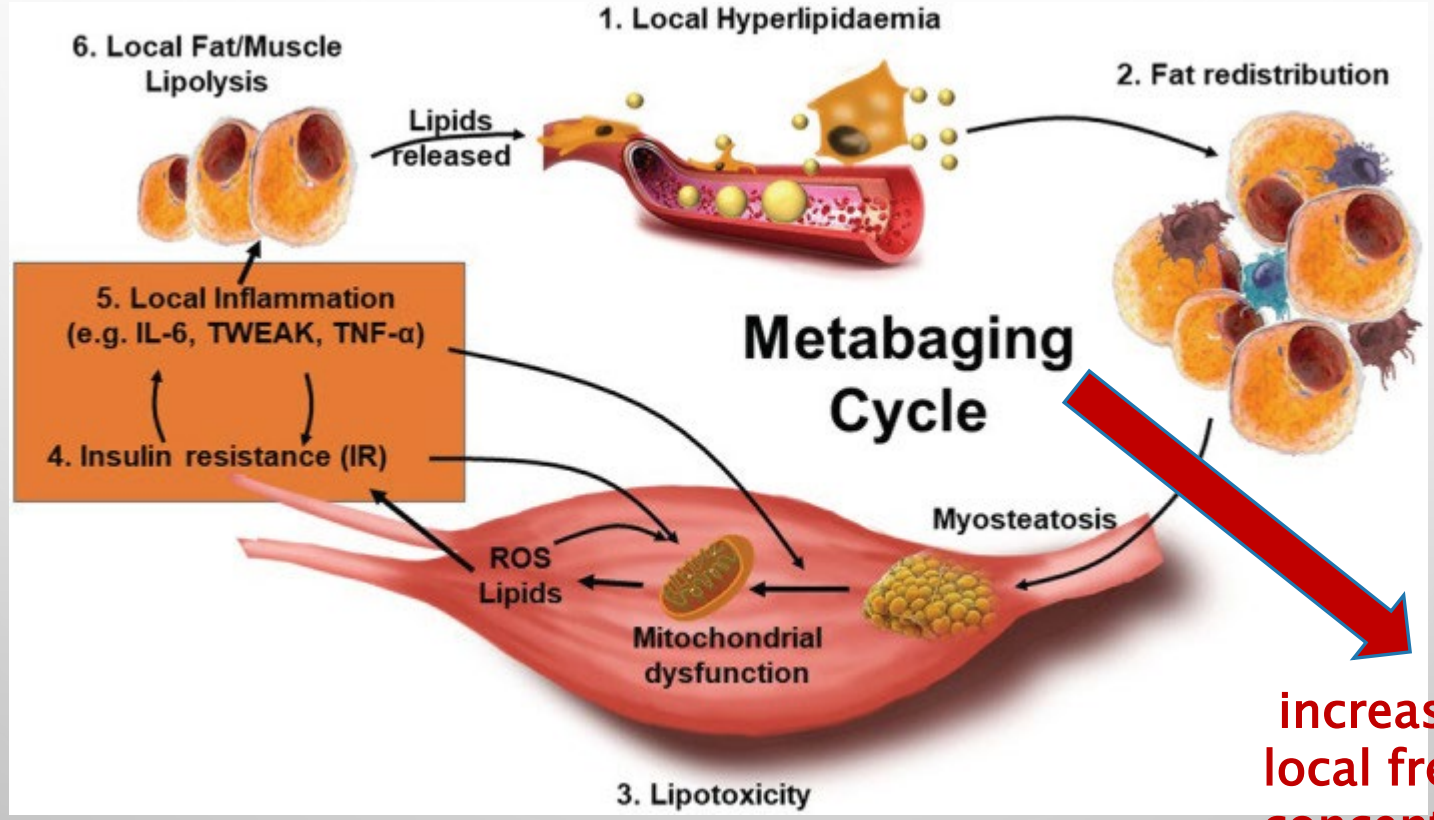
IN CONTRAST, CALORIC RESTRICTION PROMOTES SELF-RENEWAL AND PREVENTS STEM CELL EXHAUSTION.

OVERALL, OBESITY DOES NOT MIMIC AGING IN TERMS OF STEM CELLS COMPARTMENTS BUT, SIMILAR TO AGING, HAS A DISRUPTING INFLUENCE ON THEIR TISSUE MAINTENANCE FUNCTIONS.

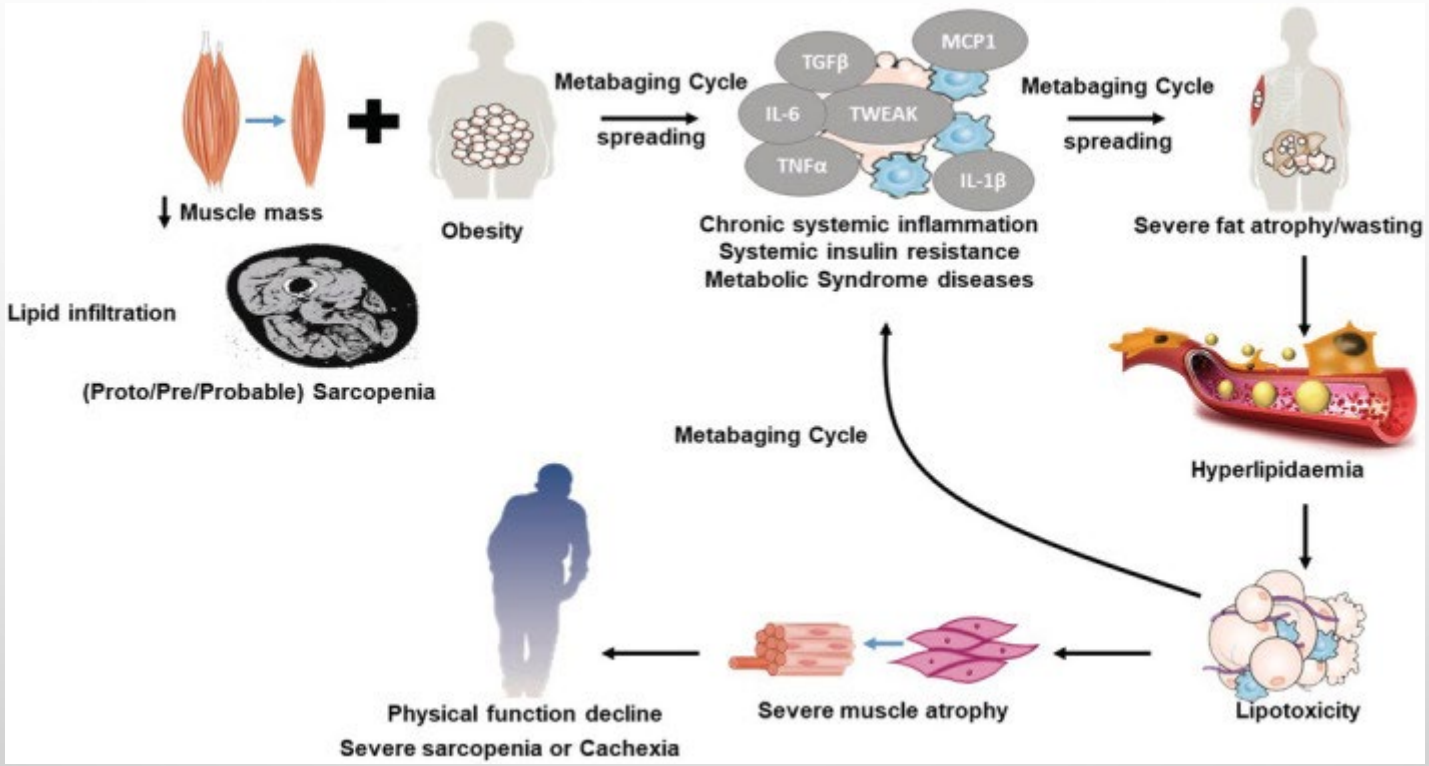
- THE OBESITY SIGNIFICANTLY DECREASES MECHANISMS ASSOCIATED WITH PROTEOME MANTEINANCE.

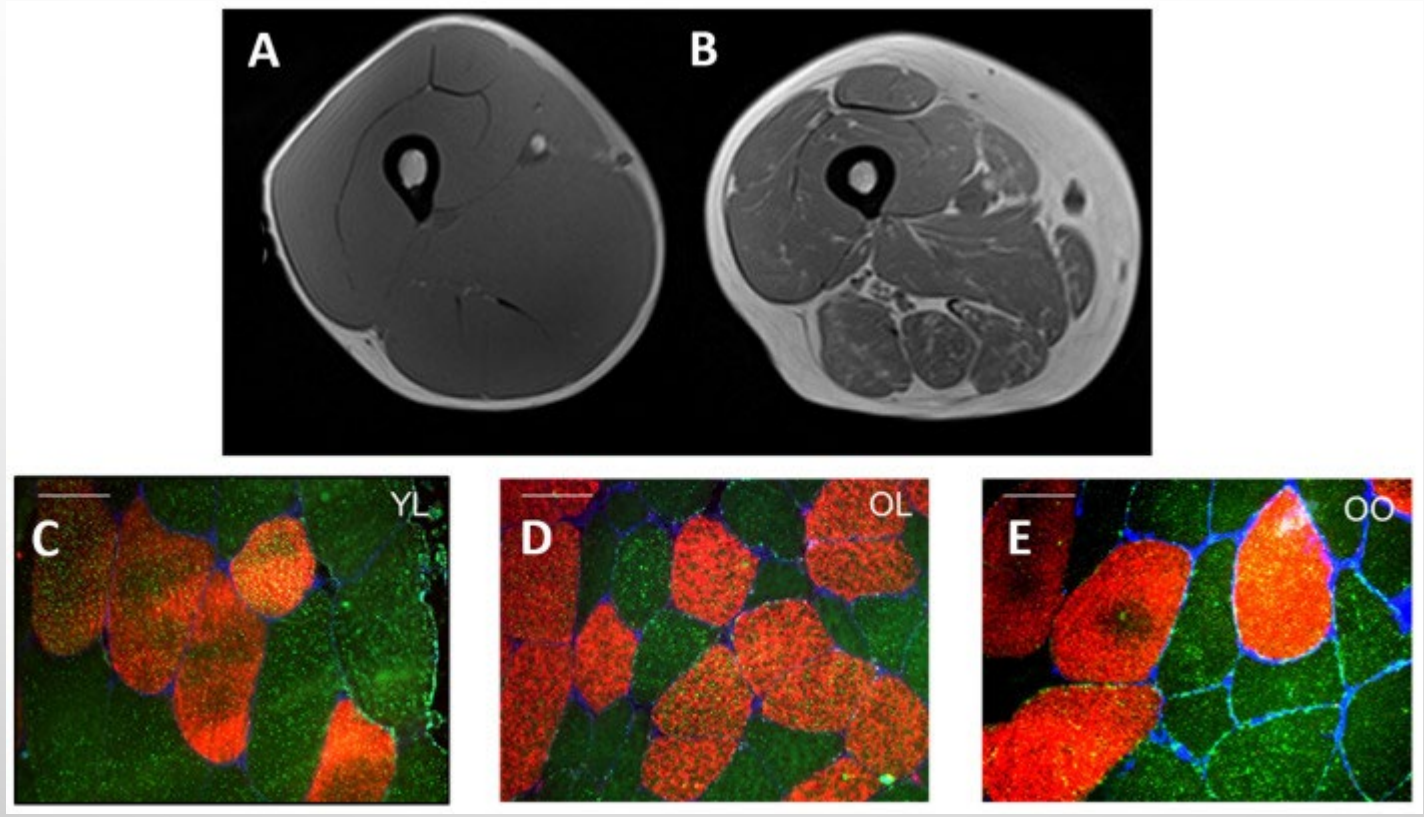
IMPACT OF OBESITY ON SKELETAL MUSCLE FUNCTION IN OLDER AGE

MYOSTEATOSIS LEADS TO SYSTEMIC INFLAMMAGING, SYSTEMIC INSULIN RESISTANCE, AND SARCOPENIC OBESITY



increasing lipolysis and local free fatty acid concentrations


Muscle mass
Obesity
Metabaging Cycle
spreading
MCP1
TGFβ
IL-6
TWEAK
TNFα
IL-1β
Chronic systemic inflammation
Systemic insulin resistance
Metabolic Syndrome diseases
Metabaging Cycle
spreading
Severe fat atrophy/wasting
Lipid infiltration
(Proto/Pre/Probable) Sarcopenia
Metabaging Cycle
Hyperlipidaemia
Physical function decline
Severe sarcopenia or Cachexia
Severe muscle atrophy
Lipotoxicity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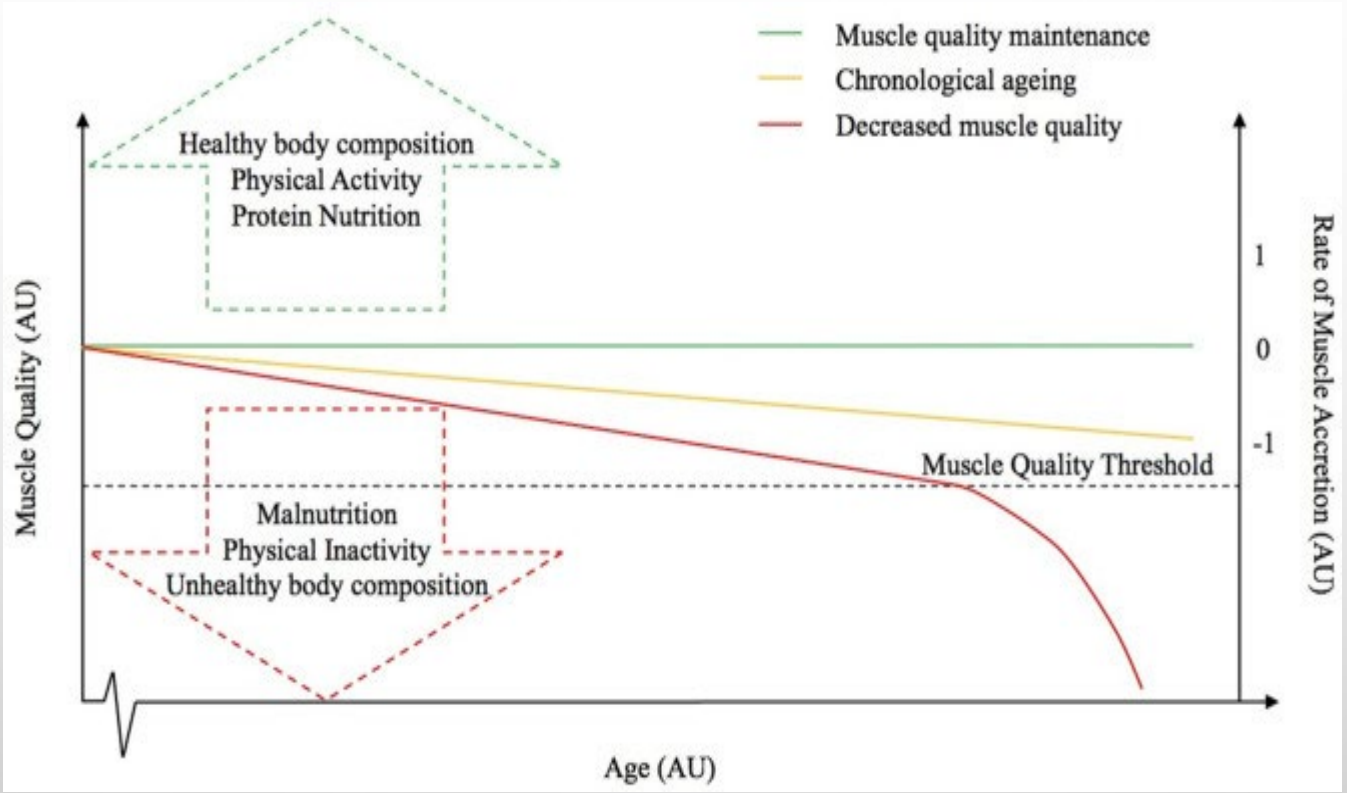
Muscle quality maintenance
Chronological ageing
Decreased muscle quality
Healthy body composition
Physical Activity
Protein Nutrition
Muscle Quality (AU)
Rate of Muscle Accretion (AU)
1
0
-1
Muscle Quality Threshold
Malnutrition
Physical Inactivity
Unhealthy body composition
Age (AU)

THE OBESITY PARADOX

THE MAJORITY OF STUDIES SUGGESTING THE EXISTENCE OF AN OBESITY PARADOX HAVE EVALUATED JUST BMI AS AN INDEX OF OBESITY.

SOME ASPECTS ARE OFTEN NOT ASSESSED OR ARE UNDERESTIMATED, IN PARTICULAR BODY COMPOSITION AND VISCERAL ADIPOSITY, SARCOPENIC OBESITY, AND CARDIO FITNESS.

SARCOPENIC OBESE MAY APPEAR AS “NORMAL” DUE TO THE MUTUAL MASKING EFFECT OF SARCOPENIA AND OBESITY.

MANY STUDIES SUPPORT THAT **CENTRAL FAT AND RELATIVE LOSS OF FAT-FREE MASS MAY BECOME RELATIVELY MORE IMPORTANT THAN BMI IN DETERMINING THE HEALTH RISK ASSOCIATED WITH OBESITY IN OLDER AGES.**

HOW DO YOU TREAT OBESITY IN THE ELDERLY PHARMACOLOGICALLY?

TO DATE:

- VERY LIMITED INFORMATION IS AVAILABLE ON THE EFFECTS OF ANTI-OBESITY DRUGS IN OLDER ADULTS.
- **ORLISTAT, TOPIRAMATE AND PHENTERMINE** HAVE SIMILAR EFFICACY IN YOUNGER PATIENTS, AS IN OLDER PATIENTS.
- THE EFFECTS ON BODY WEIGHT OF GLP-1 RECEPTOR AGONISTS **LIRAGLUTIDE AND SEMAGLUTIDE** WERE COMPARABLE TO THOSE ACHIEVED IN YOUNGER SUBJECTS, BUT THE AVAILABLE FOLLOW-UP IS INSUFFICIENT TO REACH ANY CONCLUSIONS ABOUT MEDIUM- AND LONG-TERM EFFICACY AND SAFETY.
- BALANCING THEIR SAFETY PROFILE WITH THEIR CARDIOPROTECTIVE AND GLUCOSE AND LIPID METABOLISM IMPROVING EFFECTS, **GLP-1 RECEPTOR AGONISTS MAY BE VERY RELEVANT AGENTS FOR SOME ELDERLY OBESE PATIENTS.**

PENDING QUESTIONS (I)

- SAFETY PROFILE REMAINS TO BE CLARIFIED.
- EFFECTS ON MAJOR CARDIOVASCULAR EVENTS AND GENERAL MORTALITY ARE NO ELUCIDATED.
- SAFETY DATA ARE INSUFFICIENT FOR MOST OF THE DRUGS AND EFFECTS ON MUSCLE AND BONE ARE IGNORED.
- REAL-WORLD DATA ON COMPLIANCE AND ADHERENCE WILL BE NEEDED.

PENDING QUESTIONS (II)

- THE POTENTIAL BENEFITS OF LIRAGLUTIDE ON MACEs HAS NOT BEEN PROVEN IN NON-DIABETIC OBESE PATIENTS.
- IT HAS BEEN SUGGESTED THAT THE ANTI-OBESITY EFFECTS OF THE GLP-1 RECEPTOR AGONISTS MAY BE WEAKER IN ELDERLY WITH TYPE 2 DIABETES THAN IN THOSE WITHOUT.
- THE IMPACT OF INTENTIONAL, TREATMENT-INDUCED WEIGHT LOSS ON BONE FRAGILITY IS NOT COMPLETELY CLEAR, BUT IT MAY HAVE CLINICAL RELEVANCE.
- BASED ON THE INSUFFICIENCY OF THE AVAILABLE EVIDENCE, **PHARMACOLOGICAL TREATMENT OF OBESITY IN OLDER ADULTS CANNOT BE EASILY GENERALIZED.**

SURGICAL INTERVENTION

- MANY REPORTS NOW PROVIDE EVIDENCE THAT BARIATRIC SURGERY CAN BE SAFELY PERFORMED IN OLDER PEOPLE AS THE LAST TREATMENT TIER.
- RISK–BENEFIT ISSUES SHOULD BE CONSIDERED WITH EXTREME CARE AND DISCLOSED TO CANDIDATES.
- THE SELECTION PROCESS REQUIRES GOOD PRE-SURGICAL FUNCTIONAL STATUS, INDIVIDUALIZED CONSIDERATION OF THE SEQUELS OF OBESITY, AND RELIANCE ON CENTERS THAT ARE HIGHLY EXPERIENCED IN THE SURGICAL PROCEDURE AS WELL AS SHORT-TERM AND LONG-TERM SUBSEQUENT COMPREHENSIVE CARE AND SUPPORT.

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