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UNIVERSITÀ degli STUDI di CATANIA

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XVII CONGRESSO NAZIONALE

Malattie muscolo-scheletriche e pandemia da SARS-CoV-2

CATANIA

24 - 25 settembre 2021

SESSIONE I

EFFETTI DELLA PANDEMIA SULLE MALATTIE MUSCOLO-SCHELETRICHE

Moderatori: G. Isaia - L. Malatino

15.30 Le conseguenze della pandemia sull'apparato scheletrico
I. Chiodini

15.45 Rapporti tra Vitamina D e COVID-19 - L. Gennari

16.00 COVID 19, farmaci biologici e osso - B. Frediani

16.15 Alterazioni nutrizionali nel corso della pandemia - S. Migliaccio

16.30 *Discussione interattiva tra docenti e discenti*

GISMO

Gruppo Italiano Studio
Malattie Metabolismo Osseo
organizzazione di volontariato

- Osteporosi
- Malattie Muscolo-Scheletriche
- Malattie Metaboliche
- Dolore
- Nutrizione

AGENDA

What impact on osteoporosis care have we witnessed during pandemic?

What bone health comorbidities associated with COVID-19 should we be vigilant about?

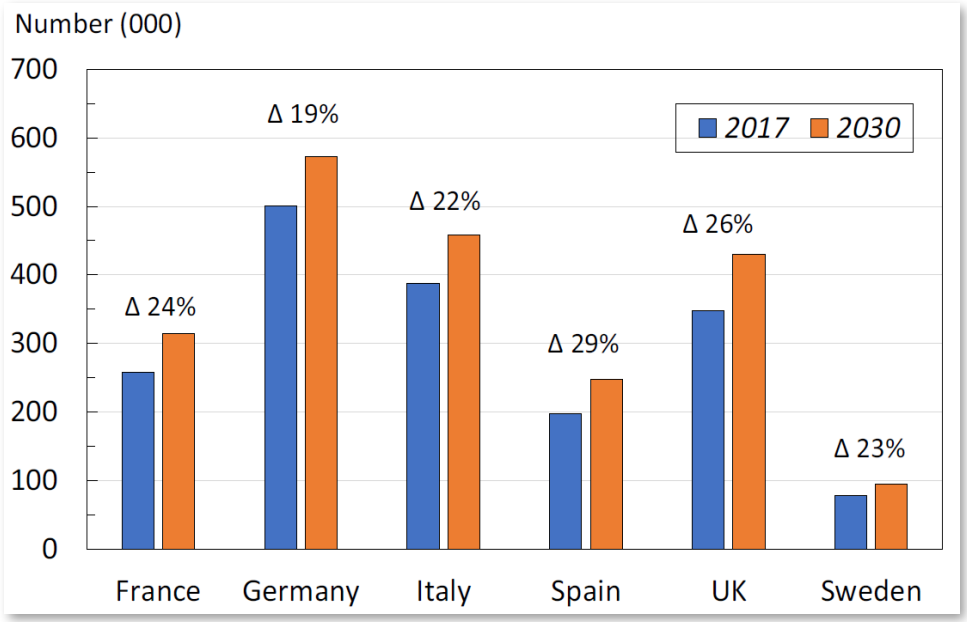
- Systemic corticosteroids
- COVID-19 and vertebral fractures
- Racial disparities and bone health
- Surgically treatable secondary osteoporosis causes during pandemic
- COVID-19 and Vitamin D
- COVID-19 and bone tissue

Osteoporosis treatment options during the pandemic

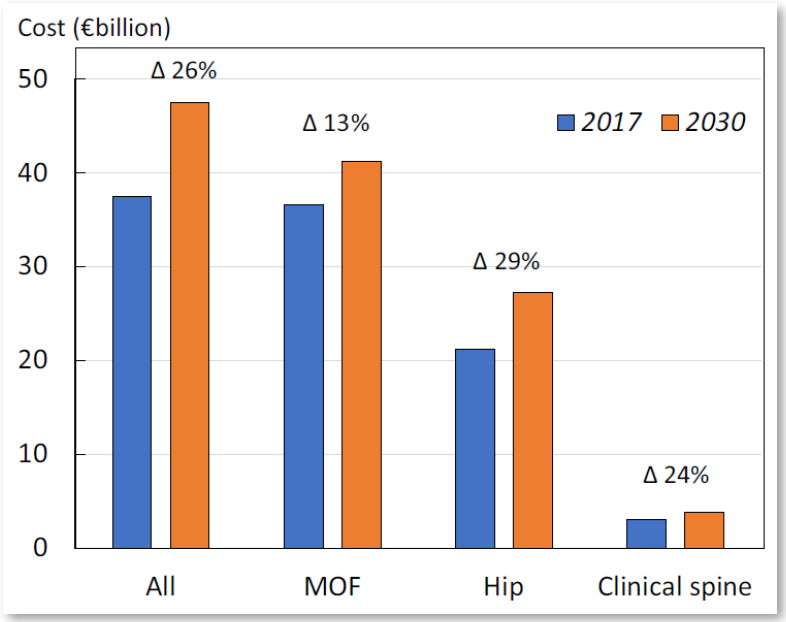
Lessons to learn

BURDEN AND MANAGEMENT OF FRAGILITY FRACTURES IN THE LARGEST FIVE COUNTRIES OF THE EUROPEAN UNION PLUS SWEDEN (EU6)

Number of fragility fractures by country in the EU6 and the projected numbers in 2030



Annual cost of fractures by site in the EU6 for 2017 and projected increase by 2030



Borgström F et al, Arch Osteoporos 2020

SYSTEMATIC, COMMUNITY-BASED SCREENING PROGRAMME OF FRACTURE RISK IN OLDER WOMEN IN THE UK IS FEASIBLE, AND COULD BE EFFECTIVE IN REDUCING HIP FRACTURES

12.483 women 70-85 from seven centers in the UK, randomized to screening or standard care, followed up for 5 years

	Control (n=6250)	Screening (n=6233)	Hazard ratio (95% CI)*	p value
Osteoporosis-related				
No fracture	5398 (86·4%)	5428 (87·1%)	..	..
Fracture	852 (13·6%)	805 (12·9%)	0·94 (0·85–1·03)	0·178
Hips				
No fracture	6032 (96·5%)	6069 (97·4%)	..	..
Fracture	218 (3·5%)	164 (2·6%)	0·72 (0·59–0·89)	0·002
All clinical				
No fracture	5248 (84·0%)	5282 (84·7%)	..	..
Fracture	1002 (16·0%)	951 (15·3%)	0·94 (0·86–1·03)	0·183
Mortality				
Survived	5725 (91·6%)	5683 (91·2%)	..	..
Died	525 (8·4%)	550 (8·8%)	1·05 (0·93–1·19)	0·436

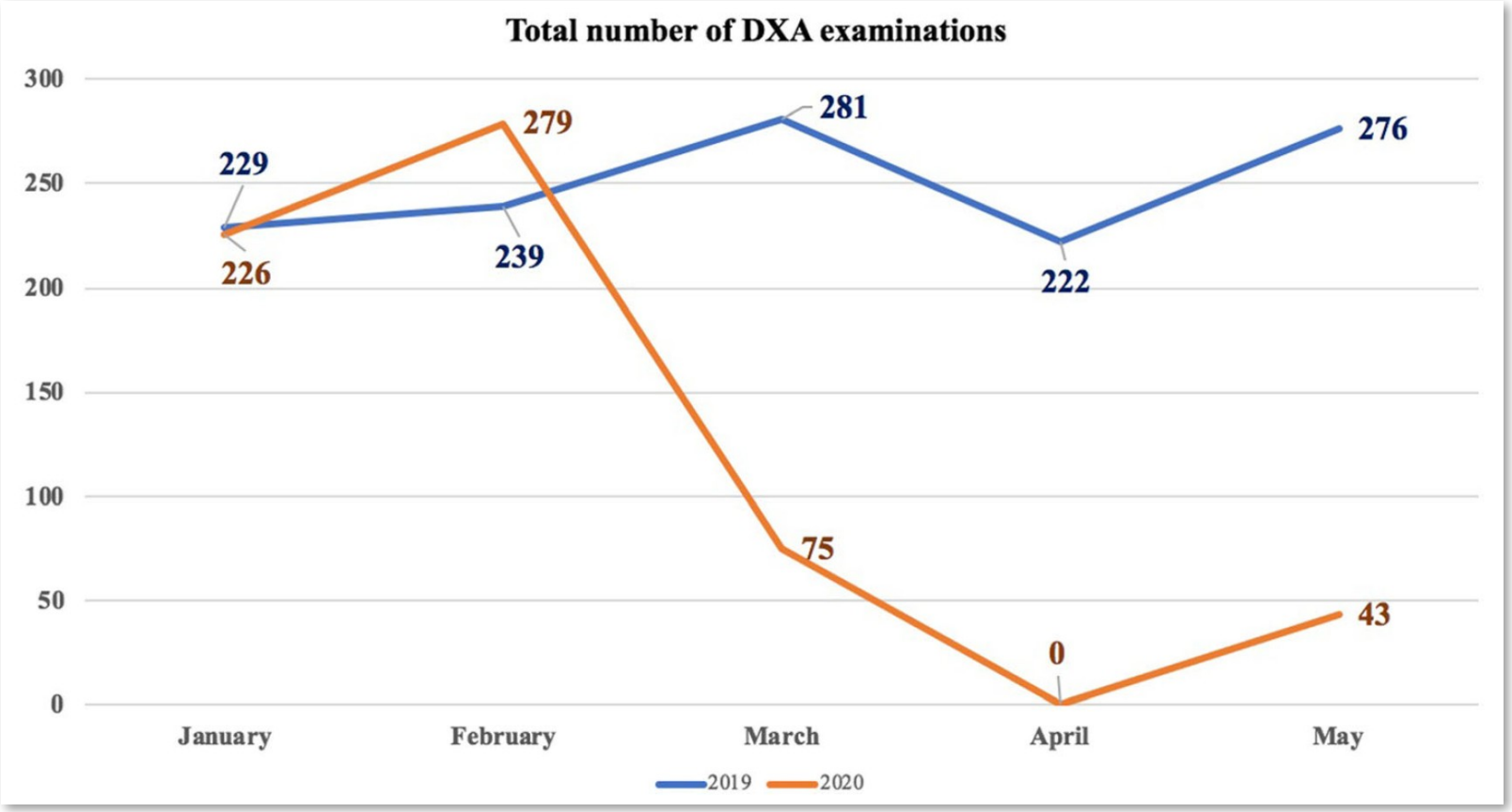
All clinical fractures included all osteoporosis-related fractures as well as fractures of the hands, feet, ankle, face, and skull. FRAX=Fracture Risk Assessment Tool. *Adjusted for recruiting region, baseline FRAX probability, and falls.

Table 3: Efficacy outcomes

Shepstone L et al, Lancet 2018

The absolute reduction in hip fracture risk was 0.9%, i.e. **111 women between the ages of 70-85 should be screened to avert a single hip fracture**

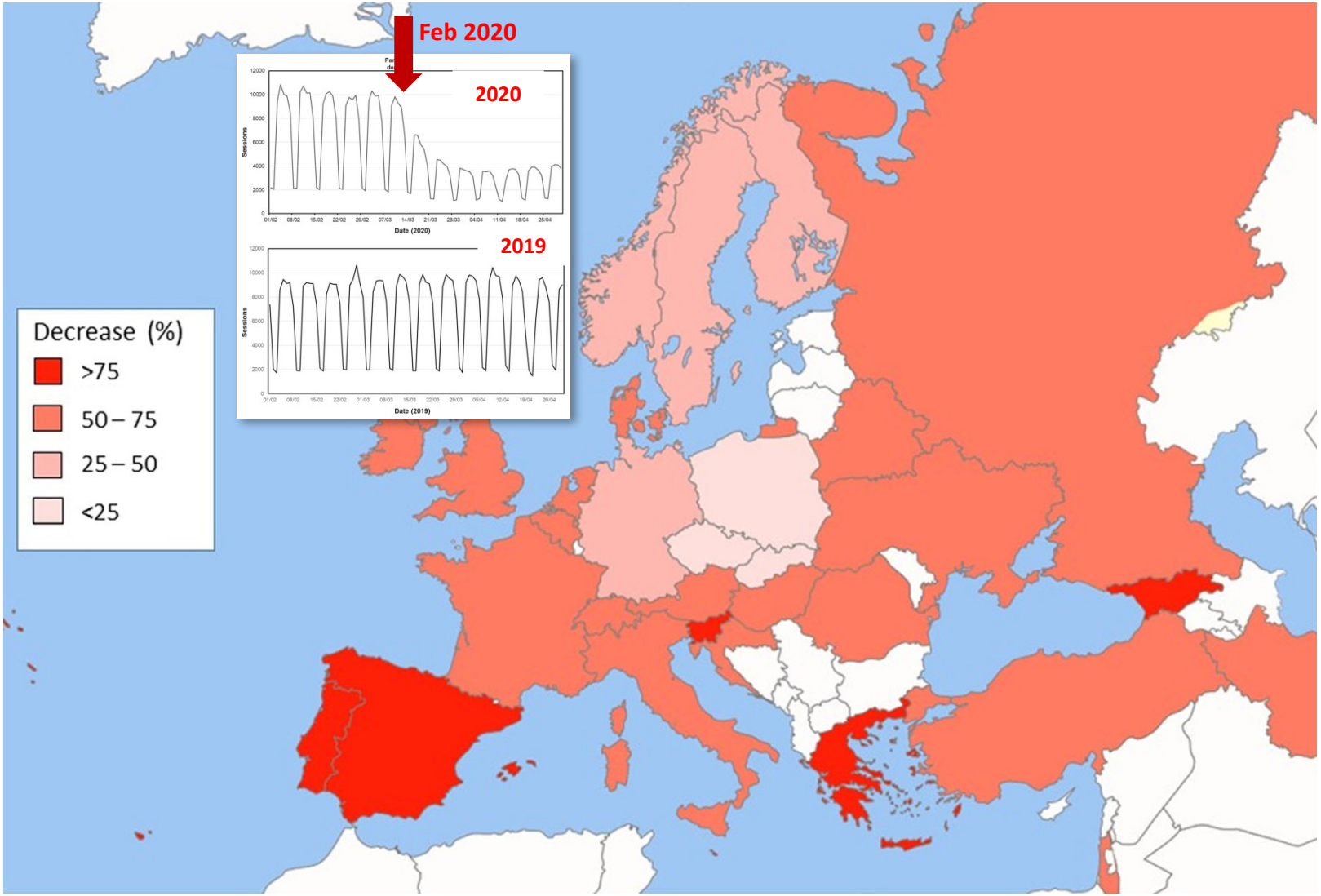
NUMBER OF DXA EXAMINATIONS PERFORMED DURING THE FIRST 4 MONTHS OF 2019 AND 2020 IN IN A NORTHERN ITALY HOSPITAL



DXA = dual energy x-ray absorptiometry

Messina C et al, Osteoporos Int 2020

DESCRIPTIVE ANALYSIS OF ACCESS TO FRAX FRACTURE RISK ONLINE TOOL FOR PREVENTION OF OSTEOPOROTIC FRACTURES



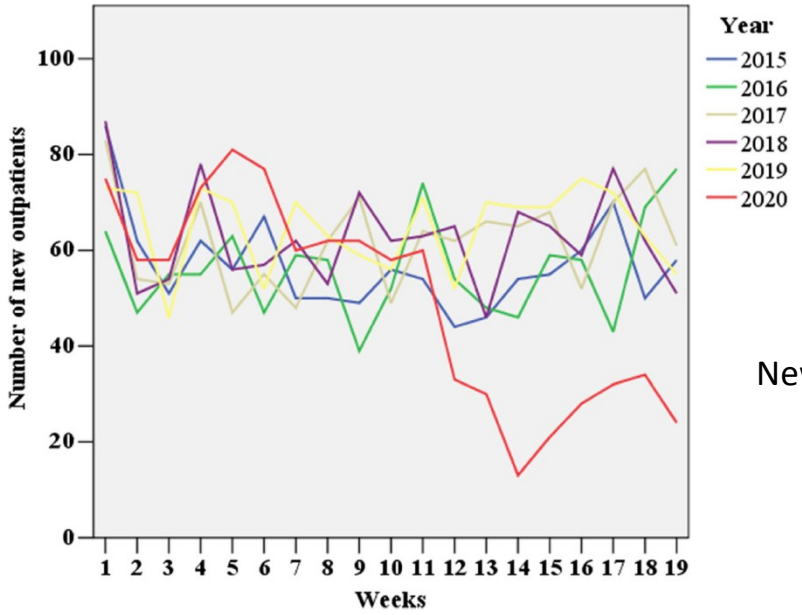
McCloskey EV et al, Osteoporos Int 2020

DURING LOCKDOWN, FEWER OUTPATIENTS ATTENDED THE FRACTURE CLINIC, FOR NON-HIP FRAGILITY FRACTURES, WHILE NO CHANGE IN INPATIENT ADMISSIONS FOR HIP FRACTURE WAS OBSERVED

	2015 (n = 393)	2016 (n = 400)	2017 (n = 459)	2018 (n = 428)	2019 (n = 473)	2020 (n = 182)	p value
Type of fracture (n (%)):							0.003
Radius, ulna or humerus	178 (45.3)	171 (42.8)	178 (38.8)	182 (42.5)	191 (40.4)	73 (40.1)	
Clavicle, scapula or shoulder	22 (5.6)	12 (3.0)	29 (6.3)	16 (3.7)	23 (4.9)	8 (4.4)	
Ankle or foot	78 (19.8)	81 (20.3)	101 (22.0)	79 (18.5)	82 (17.3)	23 (12.6)	
Tibia, fibula, patella or femur	9 (2.3)	11 (2.8)	19 (4.1)	31 (7.2)	19 (4.0)	14 (7.7)	
Other (metacarpal, hand or finger(s), …)	3 (0.8)	6 (1.5)	8 (1.7)	7 (1.6)	8 (1.7)	8 (4.4)	
No fracture	103 (26.2)	119 (29.8)	124 (27.0)	113 (26.4)	150 (31.7)	56 (30.8)	

p values are calculated using chi-square test for categorical variables and Kruskal-Wallis test for differences in median age

Abbreviations: n, number; IQ, interquartiles



New outpatients to the Fracture Clinic in the first 19 weeks of 2020, across the years 2015 to 2020

Ogliari G et al, Arch Osteoporos 2020

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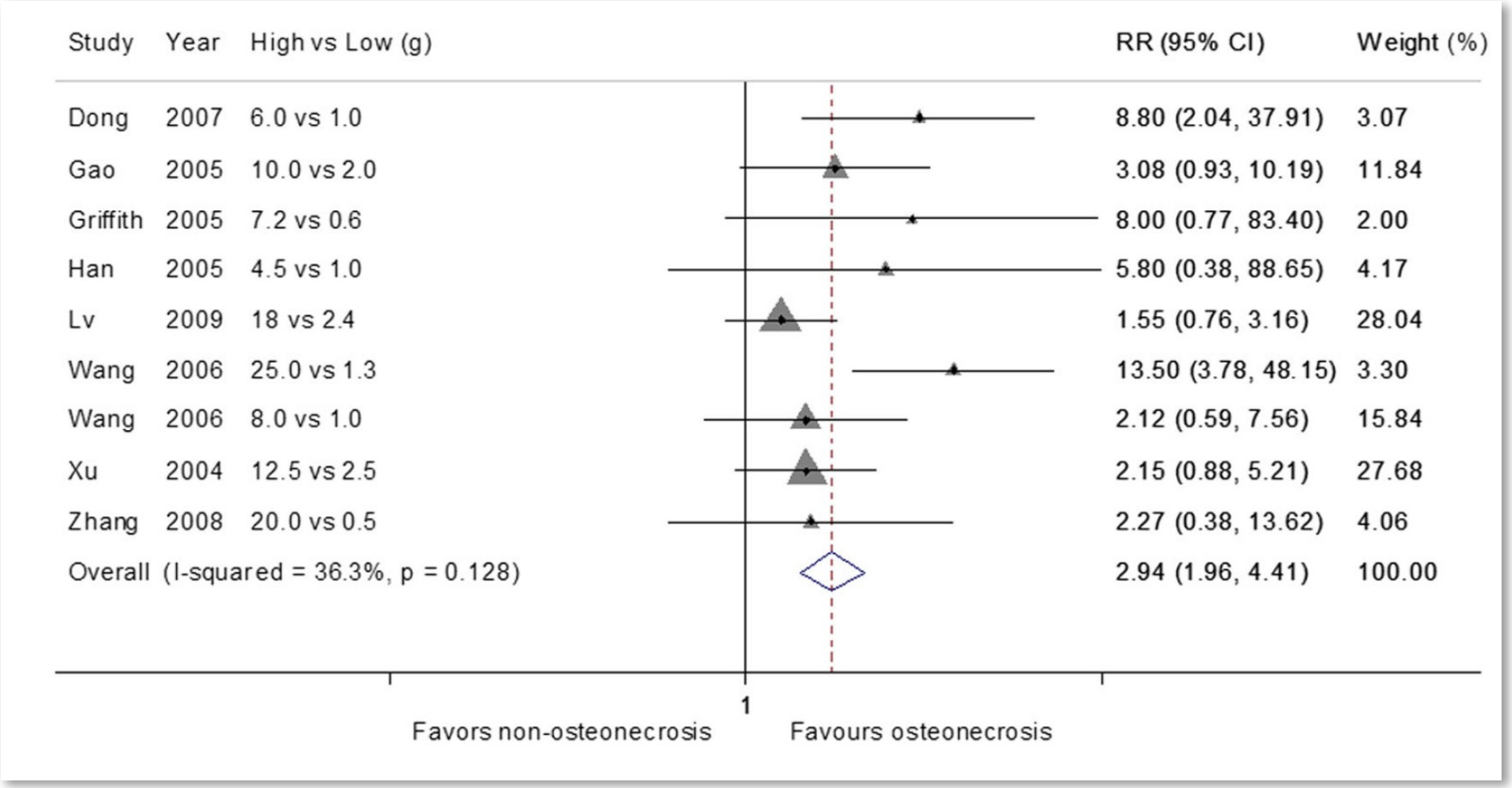
Osteoporosis treatment options during the pandemic

Lessons to learn

STEROID THERAPY AND THE RISK OF OSTEONECROSIS* IN SARS PATIENTS: A DOSE-RESPONSE META-ANALYSIS



***hips, knees, shoulders, ankles and wrists**

Zhao R et al, Osteoporos Int 2017

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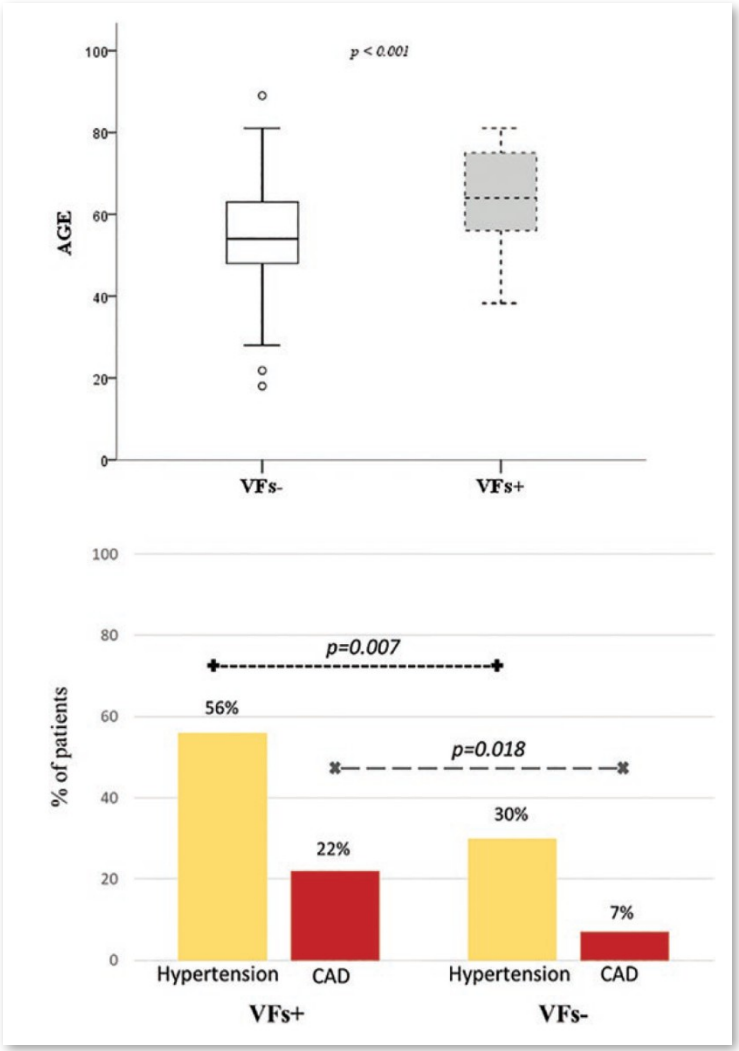
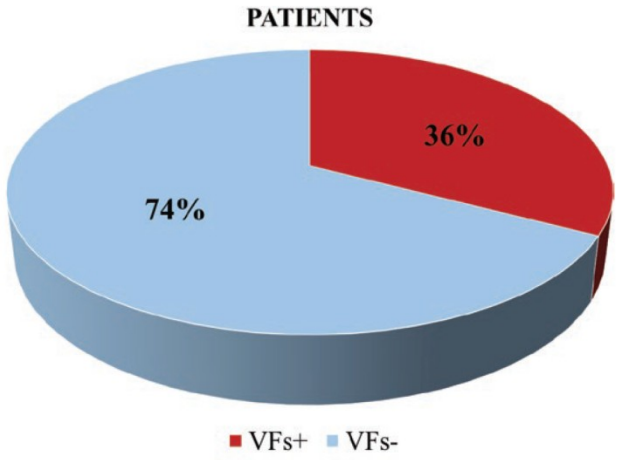
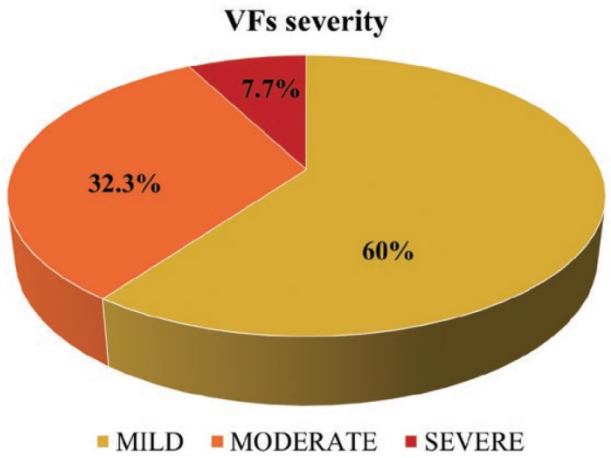
RADIOLOGICAL THORACIC VERTEBRAL FRACTURES ARE HIGHLY PREVALENT IN COVID-19 AND PREDICT DISEASE OUTCOMES



114 Hospitalized COVID-19 patients





Di Filippo L et al, JCE&M 2020

RADIOLOGICAL THORACIC VERTEBRAL FRACTURES ARE HIGHLY PREVALENT IN COVID-19 AND PREDICT DISEASE OUTCOMES

114 Hospitalized COVID-19 patients

a) Clinical outcomes in patients with or without vertebral fractures

	VFs+ group (41)	VFs– group (73)	*P* Value
Hospitalization	36 (87.8%)	54 (73.9%)	*P* = 0.08
Length of stay, days	15 [8.7-33.5]	12 [7-22.5]	*P* = 0.26
ICU admission	4 (9.7%)	9 (12.3%)	*P* = 0.77
NIMV requirement	20 (48.8%)	20 (27.4%)	*P* = 0.02
Mortality	9 (22%)	7 (9.6%)	*P* = 0.07

b) Clinical outcomes according to the degree of fracture severity

Hospitalization		
Mild (21)	20 (95%)	*P* = 0.33
Moderate (15)	12 (80%)	
Severe (5)	4 (80%)	
ICU admission		
Mild (21)	3 (14.3%)	*P* = 0.52
Moderate (15)	1 (6.6%)	
Severe (5)	0 (0%)	
NIMV requirement		*P* = 0.6
Mild (21)	11 (52.4%)	
Moderate (15)	6 (40%)	
Severe (5)	3 (60%)	
Mortality		
Mild (21)	5 (23.8%)	*P* = 0.04
Moderate (15)	1 (6.6%)	
Severe (5)	3 (60%)	

VFx may integrate the cardiorespiratory risk of COVID-19 patients, being a useful and easy to measure clinical marker of fragility and poor prognosis

Di Filippo L et al, JCE&M 2020

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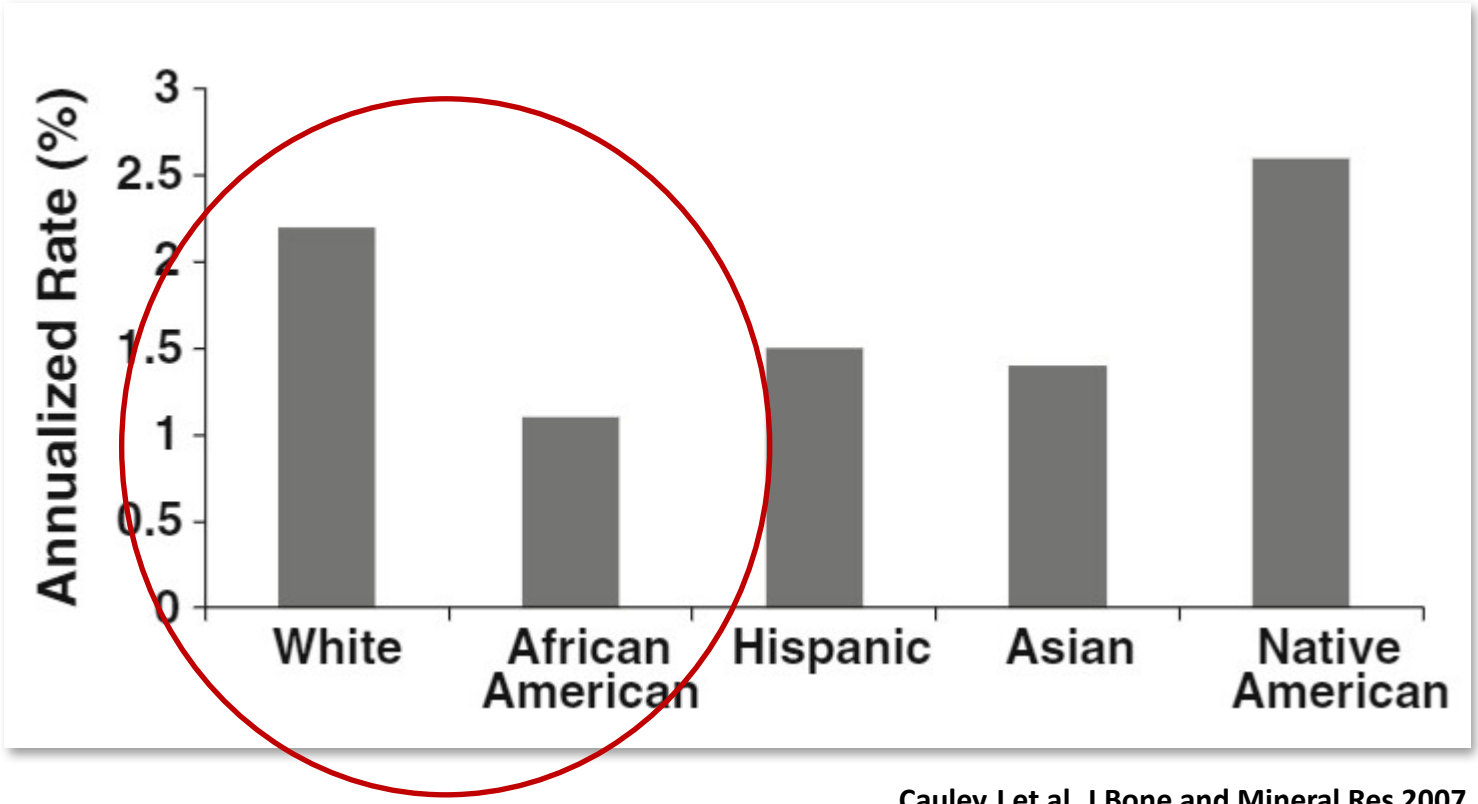
Lessons to learn

ANNUALIZED RATES OF FRACTURE BY RACE/ETHNICITY ACCORDING TO THE WOMEN'S HEALTH INITIATIVE OBSERVATIONAL STUDY

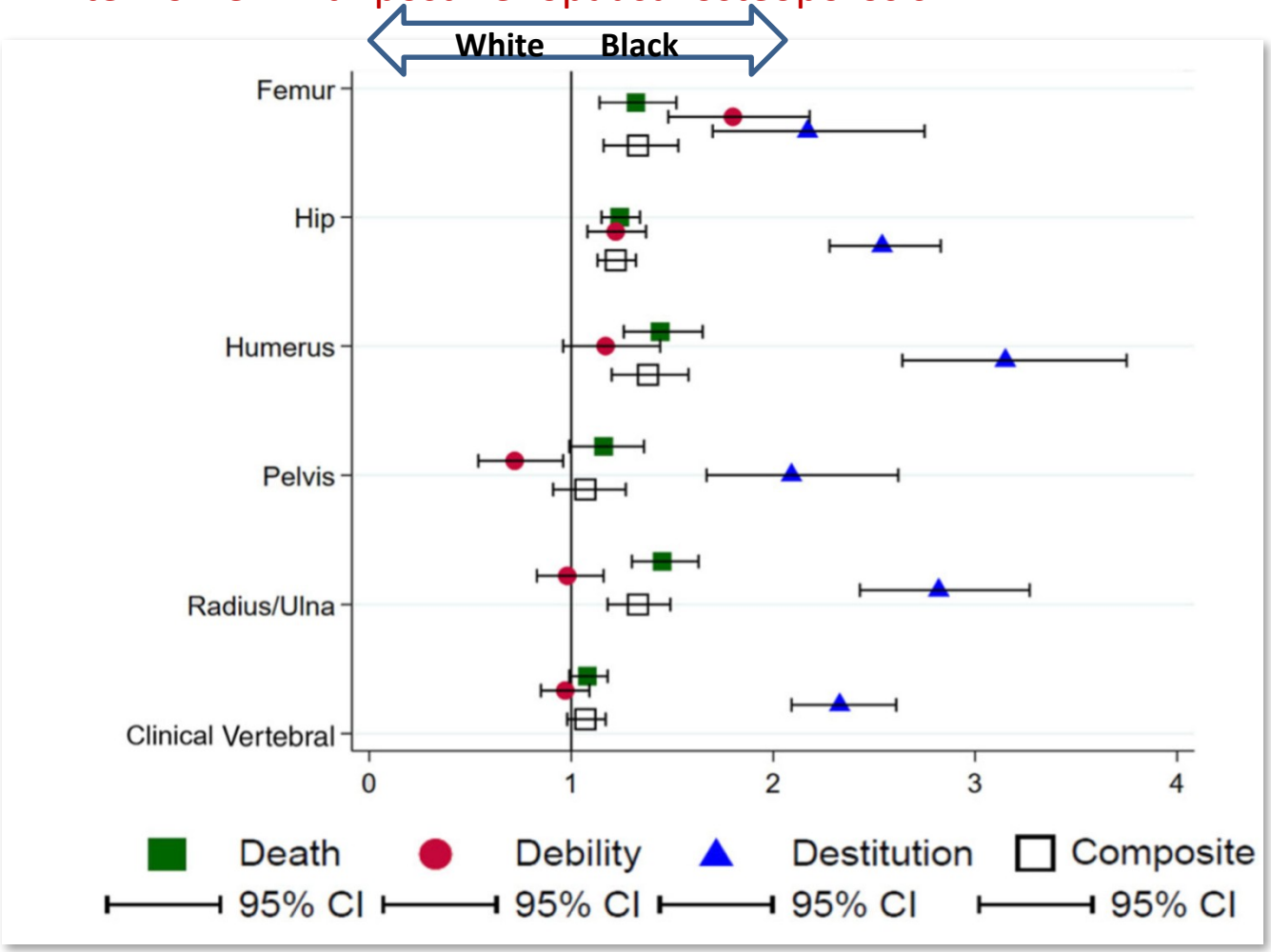


Cauley J et al, J Bone and Mineral Res 2007

RACIAL DISPARITIES EXIST IN OUTCOMES AFTER MAJOR FRAGILITY FRACTURES

Incidence rate ratio of post-fracture outcomes by fracture type in black women compared to white women with postmenopausal osteoporosis.

To the right of the line of unity (1), a higher incidence rate of post-fracture outcomes in black women compared with white women; to the left of the line, a lower incidence rate of post-fracture outcomes in black women compared with white women.



Wright NC et al, J Am Ger Soc 2020

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Lessons to learn

Endocrine surgery in the Coronavirus disease 2019 pandemic: Surgical Triage Guidelines

1.1 | Phase I

Few COVID-19 patients, hospital resources not exhausted, institution still has ICU ventilator capacity and COVID-19 trajectory not in rapid escalation phase.

Surgery restricted to patients likely to have survivorship compromised if surgery not performed within next 3 months.

Surgical cases that need to be performed as soon as feasible:

- Thyroid cancer requiring acute airway management
- Resectable anaplastic or poorly differentiated thyroid cancer without *BRAFV600E* mutation*
- Progressive/clinically aggressive differentiated or medullary thyroid cancer
- Large suspected thyroid malignancy with documented progression
- Large goiters with significant symptomatic airway compression**
- Suspected parathyroid carcinoma with significant symptomatic hypercalcemia
- Suspected adrenocortical carcinoma
- Medically uncontrolled hyperfunctioning endocrine tumors

Surgical cases that can be safely deferred:

- Differentiated thyroid cancer***
- Medullary thyroid cancer***
- Indeterminate thyroid nodules without documented progression
- Thyroid goiters**
- Primary hyperparathyroidism
- Medically controlled hyperfunctioning endocrine tumors
- Incidental, nonfunctional adrenal lesions

Jozaghi Y et al, Head & Neck 2020

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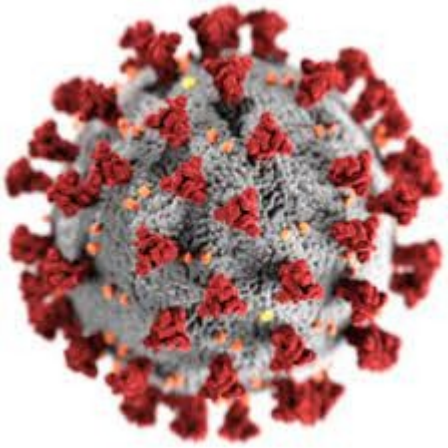
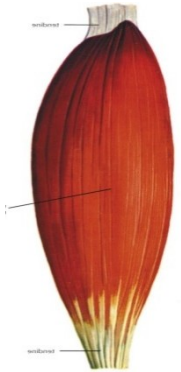
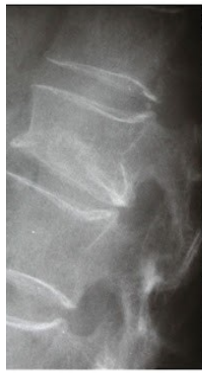
Lessons to learn

OSTEOPOROSIS AND COVID-19

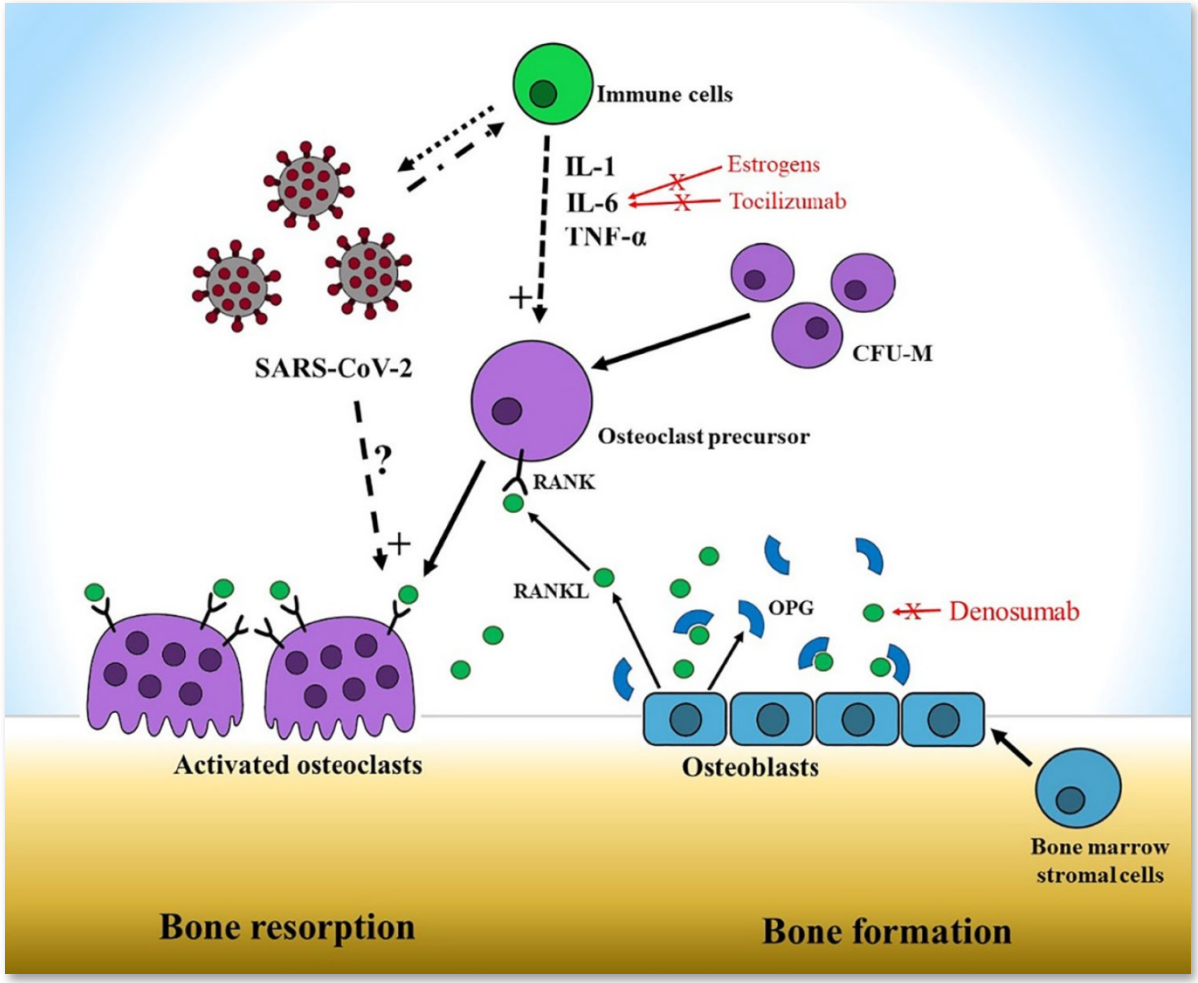


Inflammation, reduced mobilization, muscle wasting, breathing difficulties





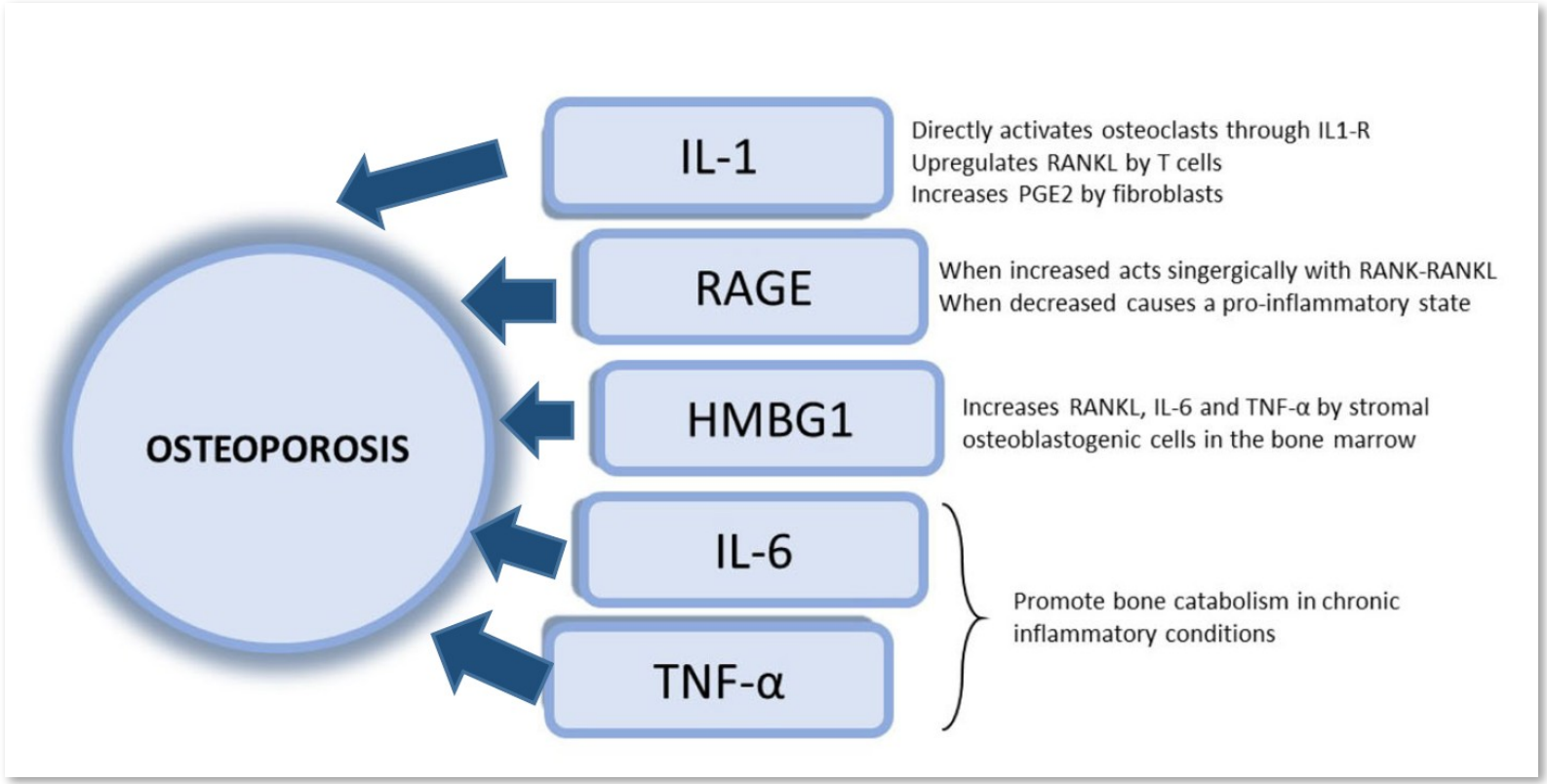
BONE METABOLISM IN SARS-COV-2 DISEASE: POSSIBLE OSTEOIMMUNOLOGY AND GENDER IMPLICATIONS



Salvio G et al, Clin Rev Bone Mineral Metab 2020

BONE METABOLISM IN SARS-COV-2 DISEASE: INFLAMMAGING

RAGE: receptor for advanced glycation end products
HMGB1: high mobility group box 1 protein



Salvio G et al, Clin Rev Bone Mineral Metab 2020

SEX BIAS IN INFECTIOUS DISEASES, INFLAMMATORY DISEASES AND CANCERS

Immune component	Characteristic	Sex difference
Sex differences in the innate immune system		
TLR pathways	TLR pathway gene expression	Higher in females
	TLR7 expression	Higher in females
	IL-10 production by TLR9-stimulated PBMCs	Higher in males
APCs	APC efficiency	Higher in females
Dendritic cells	TLR7 activity	Higher in females
	Type 1 interferon activity	Higher in females
Macrophages	TLR4 expression	Higher in males
	Activation	Higher in females
	Phagocytic capacity	Higher in females
	Pro-inflammatory cytokine production	Higher in males
	IL-10 production	Higher in females
Neutrophils	Phagocytic capacity	Higher in females
	TLR expression	Higher in males
NK cells	NK cell numbers	Higher in males

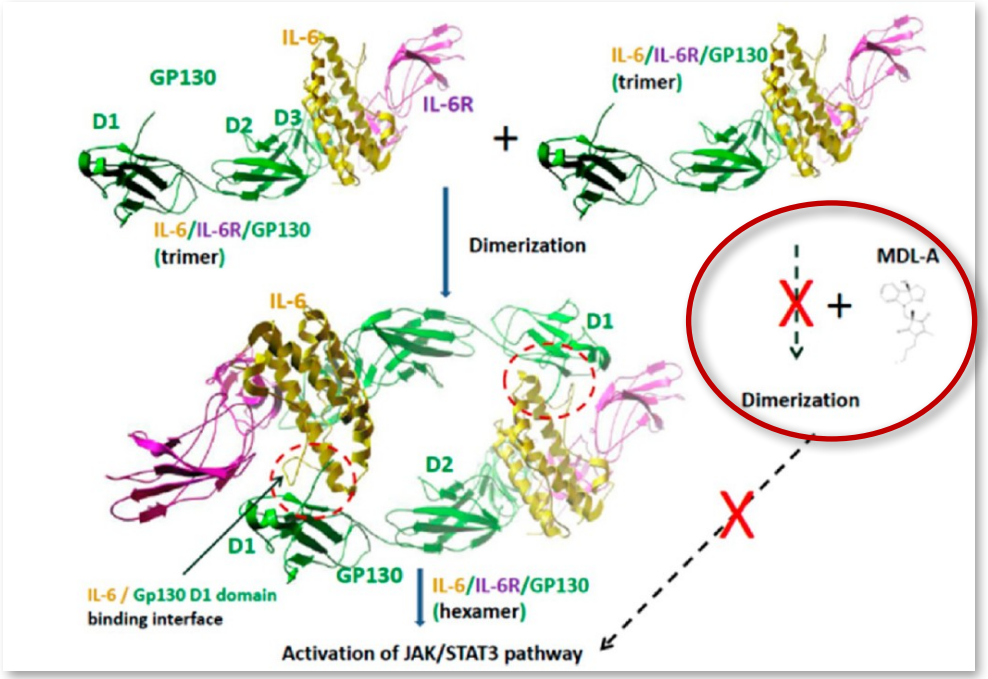
Immune component	Characteristic	Sex difference
Sex differences in the adaptive immune system		
Thymus	Size of thymus	Larger in males
T cells	$CD4^+$ T cell counts	Higher in females
	CD4/CD8 T cell ratio	Higher in females
	$CD8^+$ T cell counts	Higher in males
	Number of activated T cells	Higher in females
	T cell proliferation	Greater in females
	Cytotoxic T cells	Increased cytotoxic activity in females
	T_H1 versus T_H2 cell bias	T_H2 cell bias in females, T_H1 cell bias in males
	T_{reg} cell numbers	Increased in males
B cells	B cell numbers	Increased in females
Immunoglobulins	Antibody production	Higher in females

APC, antigen-presenting cell; IL, interleukin; NK, natural killer; PBMCs, peripheral blood mononuclear cells; T_H, T helper; TLR, Toll-like receptor; T_{reg}, regulatory T. *Based on data from humans and rodents and primary cell cultures.

Generally, females show increased susceptibility to autoimmune disease development and males show increased susceptibility to non-reproductive malignant cancers.
Although at a less pronounced magnitude, sex differences are also seen in susceptibility to various infectious diseases. Reproductive status, including pregnancy, as well as immune-mediated pathology contributes to female-biased infectious diseases, whereas pathogen-associated damage, including delayed clearance, is associated with male-biased infectious diseases.
MERS, Middle East respiratory syndrome.

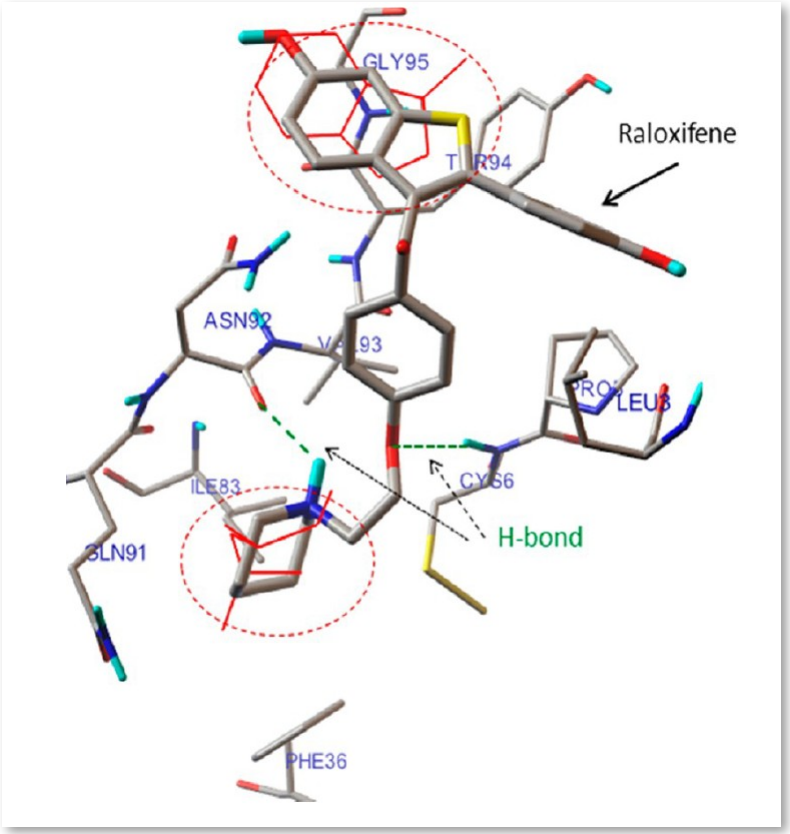
Klein SL and Flanagan KL, Nat Rev Immunol 2016

RALOXIFENE AND BAZEDOXIFENE PROMISING CANDIDATES FOR PREVENTING THE COVID-19 RELATED CYTOKINE STORM?



IL-6/GP130/STAT3 signal transduction. IL-6 first binds to IL-6Rα to form the binary complex through site I interactions. The IL-6/IL-6Rα complex then binds to D2 and D3 domains of GP130 through site II interactions and forms trimeric complex IL-6/IL-6Rα/GP130. The subsequent site III reciprocal interaction of IL-6 of one trimer with the D1 domain of P130 of the other trimer leads to homodimerization of the heterotrimer into heterohexamer complex (PDB code 1P9M).

Madindoline A (MDL-A) binds to the GP130 D1 domain and inhibits hexameric complex formation by disrupting interactions between IL-6 and the GP130 D1 domain

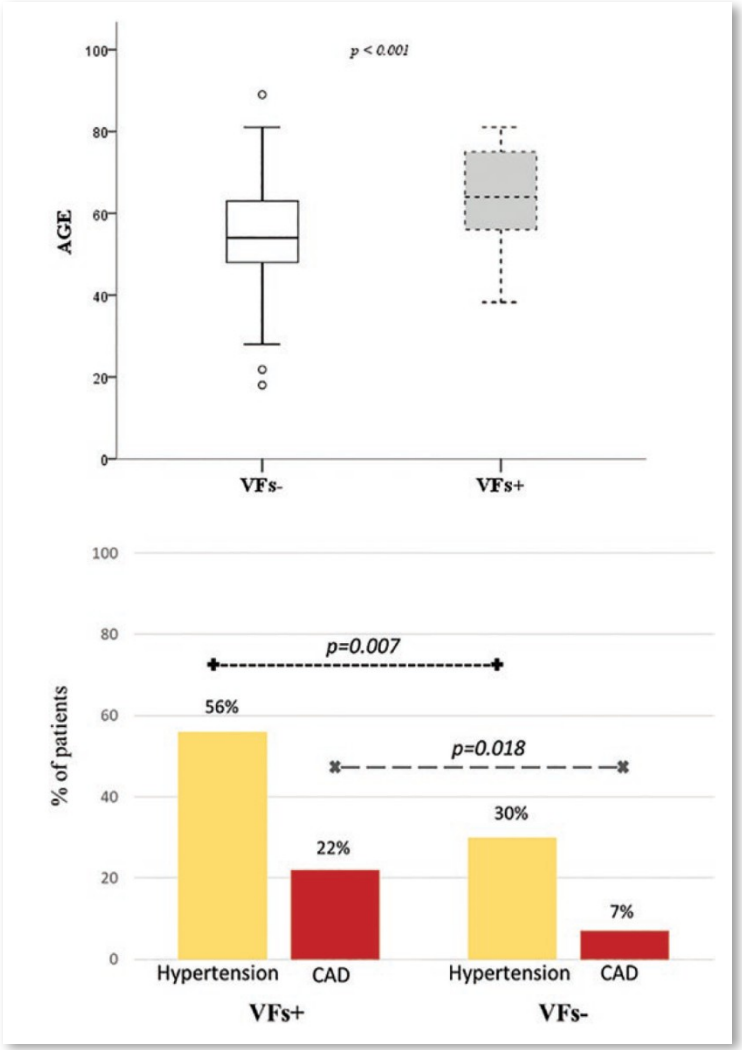


Modeling of binding interactions of raloxifene with the key residues in the active site in the GP130 D1 domain. Raloxifene is in thick ball-and-stick representation. Native residues Leu57 and Trp157 of IL-6 are thin red lines. Residues of GP130 are labeled in blue color. Asn92 and Cys6 form hydrogen bonds (green dotted lines) with RAL

Huameng Li et al, J Med Chem 2014

I. Chiodini
Dpt of Medical Biotechnology and Translational Medicine, University of Milan. Unit for Bone Metabolism Diseases and Diabetes IRCCS Istituto Auxologico Italiano

PREVALENT THORACIC VERTEBRAL FRACTURES IN COVID 19 PATIENTS ARE NOT ASSOCIATED WITH GENDER

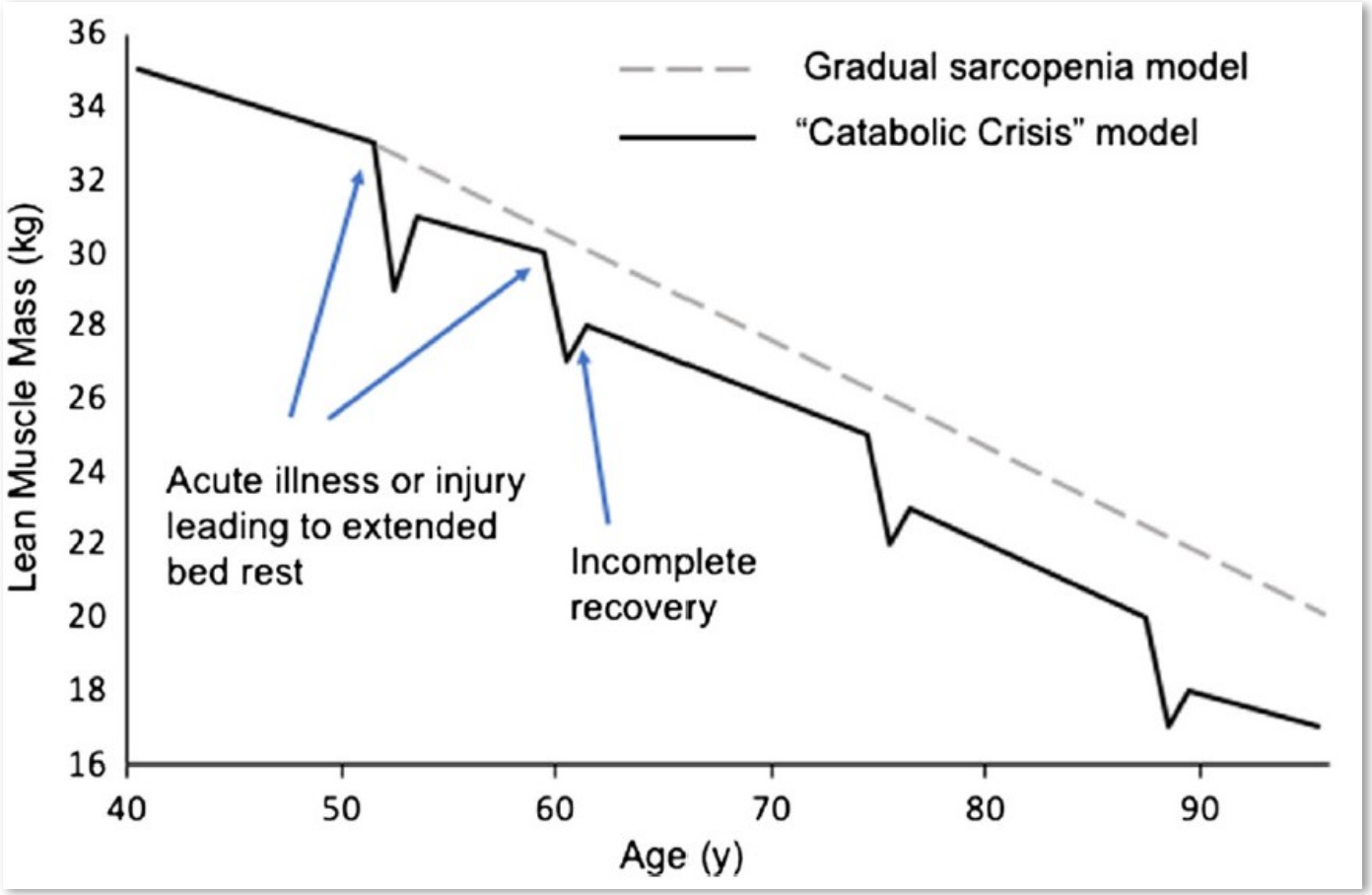


114 Hospitalized COVID-19 patients

Univariate Analysis of Predictive Factors for Vertebral Fractures		
Variables	**Odds Ratio [95% Confidence Interval]**	***P* Value**
Age	1.05 [1.02-1.09]	$P < 0.001$
Male gender	1.12 [0.47-2.68]	$P = 0.79$
BMI	1.03 [0.93-1.14]	$P = 0.53$
Hypertension	2.96 [1.34-6.55]	$P = 0.007$
Coronary artery disease	3.82 [1.19-12.34]	$P = 0.025$
Diabetes	1.31 [0.38-4.42]	$P = 0.66$
Chronic kidney disease	1.55 [0.44-5.43]	$P = 0.49$
Cancer	0.7 [0.13-3.8]	$P = 0.67$
Multivariate analysis of predictive factors for Vertebral Fractures		
Variables[a]	**Odds ratio [95% confidence interval]**	***P* Value**
Age	1.04 [1.003-1.08]	$P < 0.001$
Hypertension	1.39 [0.52-3.76]	$P = 0.51$
Coronary artery disease	1.83 [0.5-6.75]	$P = 0.36$

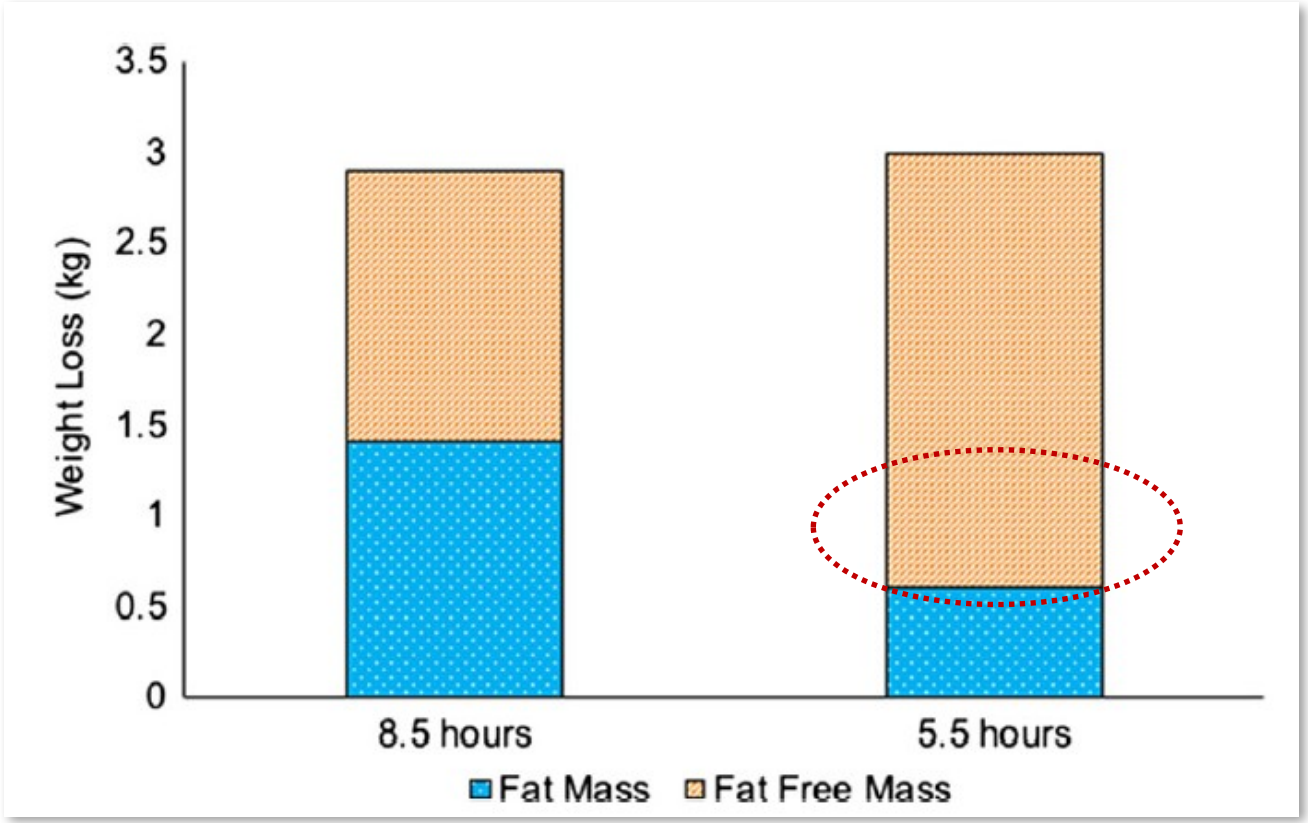
Di Filippo L et al, JCE&M 2020

POTENTIAL MODEL OF AGE ASSOCIATED MUSCLE LOSS (SARCOPENIA) EXACERBATED BY PERIODS OF EXTENDED BED REST/HOSPITALIZATION DUE TO ACUTE ILLNESS OR INJURY (CATABOLIC CRISES).



Adapted from English KL & Paddon-Jones D. Curr Opin Clin Nutr Metab Care. 2010

COMPOSITION OF CHANGES IN BODY WEIGHT DURING CALORIE RESTRICTION UNDER NORMAL AND RESTRICTED SLEEP CONDITIONS



From: Nedeltcheva AV et al. Ann Intern Med. 2010

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Lessons to learn

INITIATION OF OSTEOPOROSIS THERAPY

- Not to be delayed in patients at high risk for fracture
- Oral BISPH via a non-face-to-face (ie, telephone or video) visit
- Teriparatide/Dmab may also be considered but require additional patient training
- Patients who have fractures requiring hospital admission should be considered for osteoporosis medication initiation while hospitalized to minimize (no evidence for impaired fracture healing in patients who receive early initiation of osteoporosis treatment, including bisphosphonates)
- The administration of iv bisphosphonates may cause a post-infusion inflammatory reaction

Modified from Yu EW et al, JBMR 2020

RACCOMANDAZIONI SPECIFICHE SULLA GESTIONE DELLE TERAPIE ANTI-OSTEOPOROSI DURANTE PANDEMIA COVID-19

- Bisfosfonati orali: non interrompere o ritardare la terapia nei pazienti sottoposti a vaccinazione. Reazione di fase acuta rara e improbabile che possa essere confusa con una reazione al vaccino; inoltre non interferenza sull'efficacia dei vaccini.
- Bisfosfonati endovena: distanziare di una settimana l'infusione ev del bisfosfonato e la vaccinazione (reazione di fase acuta confondibile con effetto collaterale del vaccino. I pazienti in trattamento con ZOL possono ritardare l'infusione.
- Denosumab: distanziare iniezione e vaccinazione di 4-7 giorni (reazione nel sito di iniezione confusa con quella indotta dal vaccino oppure iniettare nel deltoide contro-laterale, addome o coscia). Non ritardare oltre 7 mesi: non vi è incremento del rischio di infezione dal COVID-19, né delle infezioni respiratorie, mentre è noto un aumento del rischio di fratture vertebrali dopo sospensione del denosumab
- Teriparatide: continuare la terapia nei pazienti sottoposti a vaccinazione.
- Raloxifene: continuare la terapia nei pazienti sottoposti a vaccinazione.
- Romosozumab: distanziare iniezione e vaccinazione di 4-7 giorni (reazione nel sito di iniezione confusa con quella indotta dal vaccino oppure iniettare nel deltoide contro-laterale, addome o coscia).

Vescini F from: Joint Guidance on COVID-19 Vaccination and Osteoporosis Management from the ASBMR, AACE, Endocrine Society, ECTS, IOF, and NOF

AGENDA

What impact on osteoporosis care have we witnessed during pandemic?

What bone health comorbidities associated with COVID-19 should we be vigilant about?

- Systemic corticosteroids
- COVID-19 and vertebral fractures
- Racial disparities and bone health
- Surgically treatable secondary osteoporosis causes during pandemic
- COVID-19 and Vitamin D
- COVID-19 and bone tissue

Osteoporosis treatment options during the pandemic

Lessons to learn

Osteoporosis International
https://doi.org/10.1007/s00198-020-05465-2

VIEWPOINTS

Identifying and managing osteoporosis before and after COVID-19: rise of the remote consultation?

Z. Paskins[1] · F. Crawford-Manning[1] · L. Bullock[2] · C. Jinks[2]

Abstract

Summary The COVID-19 pandemic is influencing methods of healthcare delivery. In this short review, we discuss the evidence for remote healthcare delivery in the context of osteoporosis.

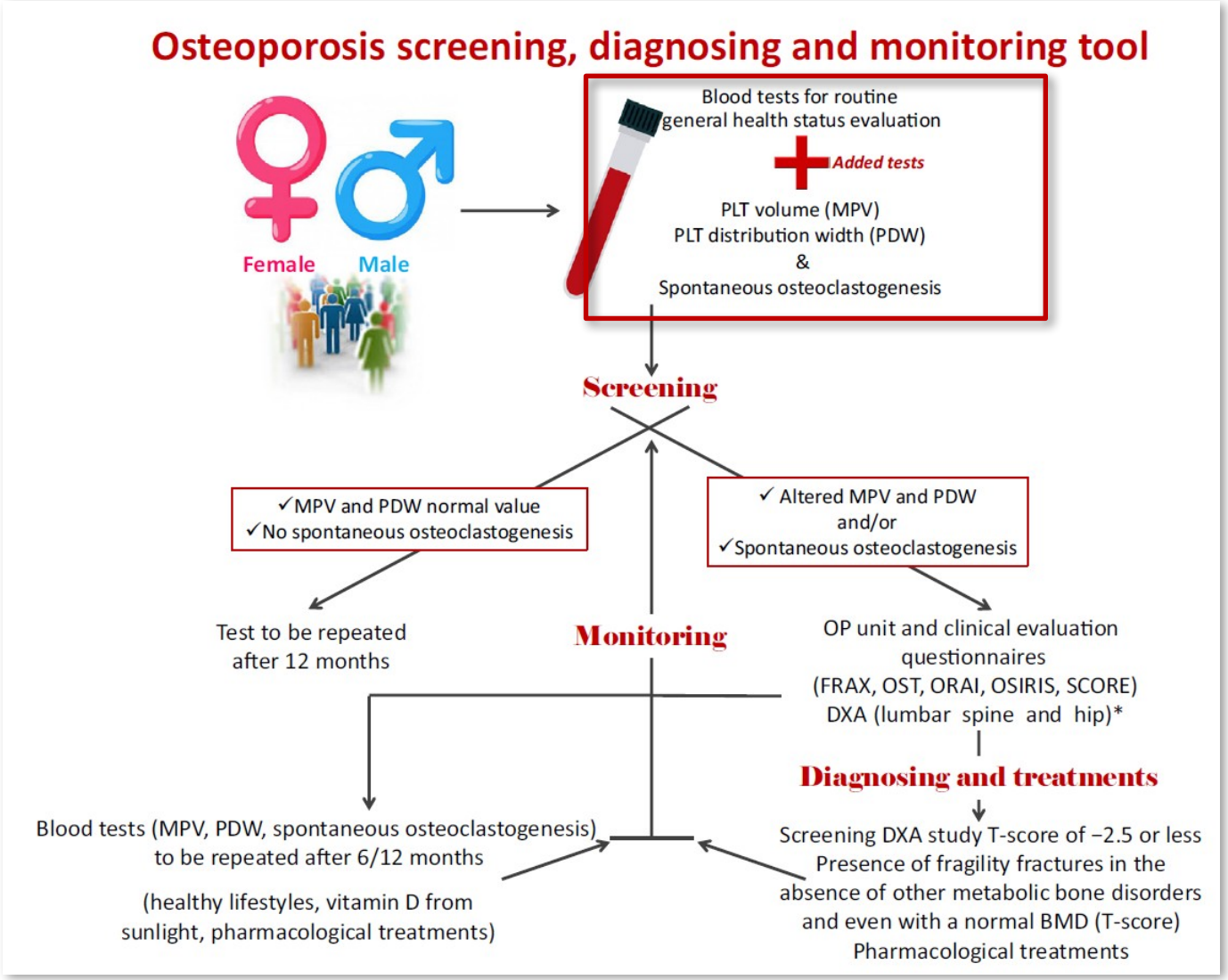
Introduction The COVID-19 pandemic has undoubtedly had, and will continue to have, a significant impact on the lives of people living with, and at risk of, osteoporosis and those caring for them. With osteoporosis outpatient and Fracture Liaison Services on pause, healthcare organisations have already moved to delivering new and follow-up consultations remotely, where staffing permits, by telephone or video.

Methods In this review, we consider different models of remote care delivery, the evidence for their use, and the possible implications of COVID-19 on osteoporosis services.

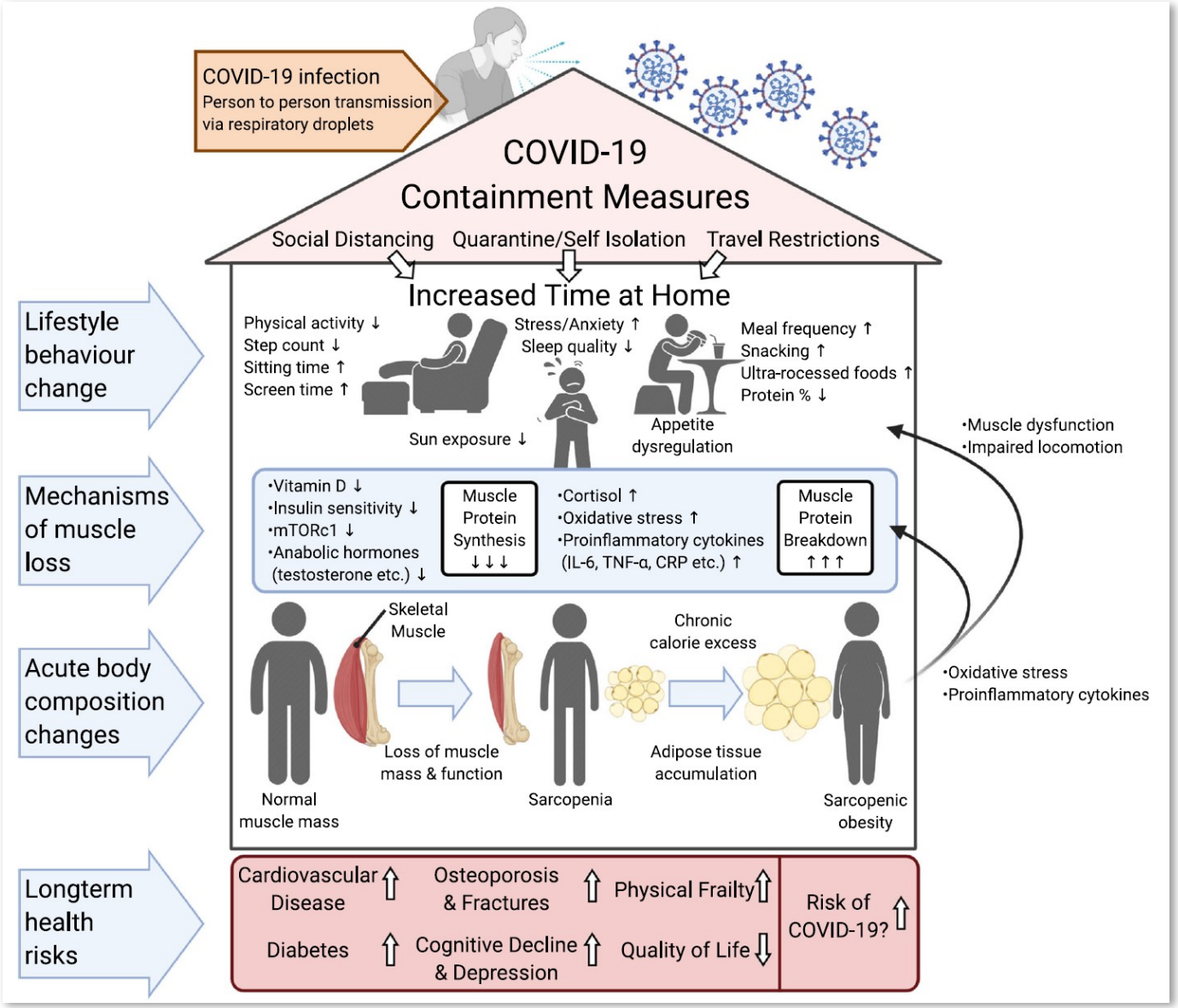
Results Telemedicine is a global term used to describe any use of telecommunication systems to deliver healthcare from a distance and encompasses a range of different scenarios from remote clinical data transfer to remote clinician-patient interactions. Across a range of conditions and contexts, there remains unclear evidence on the acceptability of telemedicine and the effect on healthcare costs. Within the context of osteoporosis management, there is some limited evidence to suggest telemedicine approaches are acceptable to patients but unclear evidence on whether telemedicine approaches support informed drug adherence. Gaps in the evidence pertain to the acceptability and benefits of using telemedicine in populations with hearing, cognitive, or visual impairments and in those with limited health literacy.

Conclusion There is an urgent need for further health service evaluation and research to address the impact of remote healthcare delivery during COVID-19 outbreak on patient care, and in the longer term, to identify acceptability and cost- and clinical-effectiveness of remote care delivery on outcomes of relevance to people living with osteoporosis.

OSTEOPOROSIS SCREENING, DIAGNOSING, AND MONITORING USING PLATELET-RELATED PARAMETERS AND SPONTANEOUS OSTEOCLASTOGENESIS



Salamanna F et al, TEM 2021



Kirwan R et al, Geroscience 2020

Il rischio maggiore….