

XVII CONGRESSO NAZIONALE

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



CATANIA 24 - 25 settembre 2021

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Metabolic syndrome



Table – Criteria for clinical diagnosis of the metabolic syndrome.	
Measure	Categorical cut points
Elevated waist circumference ^a	≥102 cm in males >88 cm in females
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator ^b) Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator ^b)	≥ 150 mg/dL (1.7 mmol/L) <40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (anti-hypertensive drug treatment in a patient with a history of hypertension is an alternate indicator) Elevated fasting glucose ^c (drug treatment of elevated glucose is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mmHg ≥100 mg/dL

Grundy SM, 2016



Management of metabolic syndrome

- Lifestyle intervention
- Caloric restriction
- Regular physical activity
- Treatment of atherogenic dyslipidemia: STATINS --- non-HDL-C <100 mg/dl (II Prev)

LDL-C <70 mg/dl non-HDL-C <130 mg/dL (I Prev) LDL-C <100 mg/dL

- Control of blood pressure
- Management of hyperglycemia
- Possible interventions on the pro-thrombotic state (low-dose methotrexate, various monoclonal antibodies, inhibitors of adhesion molecules, and colchicine)
- Reduction of pro-thrombotic state (aspirin, caloric restriction and weight loss)



Systemic changes induced by adipose tissue dysfunction



King S, 2021 (adapted)



The molecular action of MetS and its components on osteoblastogenesis and osteoclastogenesis



Chin KY, 2020



Metabolic Syndrome and Osteoporosis in Relation to Muscle Mass

Men



Non-MetS

MetS

Odds ratios (95 % confidence interval)* of combined groups of muscle mass and metabolic syndrome (MetS) for prevalent osteoporosis in Korean men and women

Combination of high muscle mass and MetS was associated with lower prevalence of osteoporosis in Korean men and women.



Metabolic syndrome and the risk of osteoporosis



MS was significantly associated with a 31 lower osteoporosis risk

Relationship between Metabolic Syndrome and Bone Health

- Positive association between metabolic syndrome and bone mineral density
- Negative association between metabolic syndrome and bone mineral density
- Sex specific relationship between metabolic syndrome and bone mineral density
- relationship between metabolic syndrome and bone fracture



Positive association between metabolic syndrome and bone mineral density

Bone Mineral Density in Adults with the Metabolic Syndrome: Analysis in a Population-Based U.S. Sample

TABLE 2. Femoral neck BMD for persons with and without the metabolic syndrome by quintile of BMI^a

	n	Group	Metabolic syndrome (n = 1773)	No metabolic syndrome (n = 6421)	P value
All subjects	8149	Unadjusted	0.83 (0.82, 0.84)	0.84 (0.84, 0.85)	0.0020
		Age and gender adjusted	0.89 (0.88, 0.89)	0.83 (0.83, 0.83)	< 0.0001
		Fully adjusted ^b	0.86 (0.85, 0.86)	0.80 (0.80, 0.80)	< 0.0001
BMI by quintile (kg/m ²)					
<25.0	3251	Unadjusted	0.69 (0.67, 0.72)	0.80 (0.80, 0.81)	< 0.0001
		Age and gender adjusted	0.82 (0.80, 0.84)	0.80 (0.79, 0.80)	0.045
		Fully adjusted ^b	0.78 (0.76 0.80)	0.77 (0.77, 0.78)	0.7
25.0 - 29.9	2900	Unadjusted	0.78 (0.77, 0.80)	0.87 (0.86, 0.87)	< 0.0001
		Age and gender adjusted	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)	0.9
		Fully adjusted ^b	0.81 (0.80, 0.82)	0.82 (0.82, 0.83)	0.3
30.0-34.9	1321	Unadjusted	0.86 (0.85, 0.87)	0.90 (0.89, 0.91)	< 0.0001
		Age and gender adjusted	0.89 (0.88, 0.90)	0.88 (0.87, 0.89)	0.3
		Fully adjusted ^b	0.92 (0.90, 0.93)	0.86 (0.85, 0.87)	0.003
≥35	722	Unadjusted	0.92 (0.91, 0.94)	0.95 (0.93, 0.97)	0.0045
		Age and gender adjusted	0.94 (0.93, 0.96)	0.94 (0.92, 0.95)	0.6
		Fully adjusted ^b	0.92 (0.90, 0.94)	0.90 (0.88, 0.92)	0.6

^a Least square mean (95% confidence interval) (g/cm²).

^b Age, gender, race, smoking, alcohol, physical activity (METs/month), self-reported health, menopause, serum 25-hydroxyvitamin D, total calcium intake, glucocorticoids, thiazide, hormone replacement therapy, statin, β -blocker use, CRP level, and comorbidity (congestive heart failure, cerebral vascular accident, COPD, and cancer).

TABLE 3. Femoral neck BMD for	persons with different number of com	ponents of the metabolic syndrome ^a
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	0	1	2	3	4	5	
No. of components	(n = 2472)	(n = 2262)	(n = 1690)	(n = 1113)	(n = 517)	(n = 143)	P value ^b
Unadjusted	0.85 (0.85, 0.86)	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.81 (0.80, 0.83)	0.82 (0.79, 0.85)	< 0.0001
Age and gender adjusted	0.80 (0.80, 0.81)	0.83 (0.83, 0.84)	0.86 (0.85, 0.87)	0.89 (0.88, 0.89)	0.89 (0.88, 0.90)	0.92 (0.90, 0.94)	< 0.0001
Fully adjusted ^c	0.78 (0.77, 0.78)	0.80 (0.79, 0.81)	0.83 (0.82, 0.84)	0.86 (0.85, 0.87)	0.86 (0.85, 0.87)	0.90 (0.88, 0.91)	< 0.0001

^a Least square mean (95% confidence interval) (g/cm²).

^b P value for trend.

^c Age, gender, race, smoking, alcohol, physical activity (METs/month), self-reported health, menopause, serum 25-hydroxyvitamin D, total calcium intake, glucocorticoids, thiazide, hormone replacement therapy, statin, β -blocker use, CRP level, and comorbidity (congestive heart failure, cerebral vascular accident, COPD, and cancer).



Positive association between metabolic syndrome and bone mineral density

Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study

Table 3 Mean (SE) bone mineral density by metabolic		Men			Women		
syndrome status		YES (n=98) Mean (SE)	NO (n=319) Mean (SE)	P value	YES (n=122) Mean (SE)	NO (n=549) Mean (SE)	P value
	Total hip						
	Age adjusted	.997 (.014)	.942 (.008)	0.001	.822 (.012)	.788 (.006)	0.01
	Age + BMI	.936 (.014)	.960 (.007)	0.14	.788 (.012)	.798 (.005)	0.14
	All covariates	.937 (.014)	.960 (.007)	0.16	.788 (.012)	.797 (.005)	0.51
	Femoral neck						
	Age adjusted	.784 (.013)	.755 (.007)	0.05	.673 (.010)	.652 (.005)	0.06
	Age + BMI	.735 (.013)	.770 (.007)	0.025	.644 (.011)	.659 (.005)	0.21
	All covariates	.737 (.013)	.769 (.007)	0.038	.653 (.011)	.658 (.005)	0.65
All covariates: age, BML alco-	Lumbar spine						
hol, exercise, smoking status,	Age adjusted	1.179 (.021)	1.092 (.012)	< 0.001	.973 (.017)	.931 (.008)	0.030
calcium supplements, and	Age + BMI	1.104 (.022)	1.115 (.011)	0.67	.925 (.018)	.942 (.006)	0.42
current estrogen use at baseline in women	All covariates	1.104 (.022)	1.115 (.011)	0.67	.939 (018)	.943 (.008)	0.86

The positive association between MetS and BMD was driven by mechanical loading reflected through BMI. This observation is evident when BMI-adjustment attenuates or reverses the association between MetS and BMD

D. von Muhlen, 2007



metabolic syndrome

Negative association between metabolic syndrome and bone mineral density

The relationship between low bone mass and metabolic syndrome in Korean women

	Metabolic syndrome				
	Without (<i>n</i> =1,964)	With (<i>n</i> =511)	p value		
Unadjusted	0.925 ± 0.004	0.858±0.007	0.000		
Age, height, weight adjusted	0.915 ± 0.003	0.895 ± 0.007	0.009		
All covariates adjusted	0.914 ± 0.003	0.898 ± 0.007	0.031		

Table 3 Vertebral BMD (g/cm²) of women with or without the

Values are expressed as least square mean \pm SE. *p* value is calculated by analysis of covariance (ANCOVA). All covariates: age, weight, height, alcohol consumption, exercise, menopause



Fig. 1 Vertebral BMD (g/cm^2) according to the number of the components of metabolic syndrome. p value is calculated by analysis of covariance (ANCOVA). Vertebral BMD levels are adjusted for age, weight, and height



Negative association between metabolic syndrome and bone mineral density

Metabolic syndrome is associated to an increased risk of low bone mineral density in free-living women with suspected osteoporosis



Rendina D, 2021



Sex specific relationship between metabolic syndrome and bone mineral density

Association between Metabolic Syndrome and Bone Mineral Density – Data from the Berlin Aging Study II (BASE-II)

	BMD	Model 1		Model 2		Model 3	
MALES		β	р	β	р	β	р
	Spine Hip Femur	-0.003 -0.071 -0.0007	0.98 0.339 0.929	-0.01 -0.067 -0.005	0.94 0.378 0.953	-0.025 0.91 -0.45	0.86 0.256 0.586

 $\beta = \beta$ -Coefficient. Model 1 was corrected for age, weight and height. Model 2 was additionally corrected for physical activity, smoking pack-years and alcohol consumption. Model 3 was additionally corrected for GFR, TSH, vitamin D₃, CRP and folic acid serum levels.

BMD	Model 1		Model 2		Model 3	
FEMALES	β	р	β	р	β	р
Spine Hip Femur	0.293 0.165 0.153	0.021 0.066 0.077	0.313 0.175 0.165	0.0152 0.054 0.06	0.369 0.202 0.161	0.005 0.028 0.078

 $\beta = \beta$ -Coefficient. Model 1 was corrected for age, weight and height. Model 2 was additionally corrected for physical activity, smoking pack-years and alcohol consumption. Model 3 was additionally corrected for GFR, TSH, vitamin D₃, CRP and folic acid serum levels.



Sex specific relationship between metabolic syndrome and bone mineral density

Metabolic syndrome and bone metabolism: the Camargo Cohort Study

	Metabolic syndrome								
		Men			Women	en			
	Yes $(n = 138)$	No (n = 357)	Р	Yes $(n = 307)$	No (n = 706)	Р			
Lumbar spine									
Unadjusted	1.034 (0.014)	1.014 (0.008)	0.2	0.935 (0.008)	0.912 (0.005)	0.02			
Age adjusted	1.033 (0.014)	1.014 (0.008)	0.3	0.942 (0.008)	0.909 (0.005)	0.001			
\rightarrow Age + BMI	1.018 (0.014)	1.020 (0.009)	0.9	0.925 (0.008)	0.917 (0.004)	0.5			
Femoral neck									
Unadjusted	0.829 (0.011)	0.808 (0.007)	0.1	0.740 (0.007)	0.715 (0.005)	0.002			
Age adjusted	0.829 (0.011)	0.808 (0.007)	0.1	0.755 (0.007)	0.709 (0.004)	< 0.0001			
\rightarrow Age + BMI	0.805 (0.011)	0.817 (0.006)	0.3	0.732 (0.006)	0.719 (0.004)	0.1			
Total hip									
Unadjusted	0.992(0.011)	0.971 (0.007)	0.1	0.871 (0.007)	0.838 (0.005)	< 0.0001			
Age adjusted	0.992 (0.011)	0.970 (0.007)	0.1	0.886 (0.007)	0.831 (0.004)	< 0.0001			
Age + BMI	0.969 (0.011)	0.979 (0.006)	0.4	0.859 (0.007)	0.843 (0.004)	0.047			

TABLE 2. Bone mineral density findings by sex and metabolic syndrome status

Data are presented as mean (SE).

BMI, body mass index.



Sex specific relationship between metabolic syndrome and bone mineral density

Low bone mineral density is associated with metabolic syndrome in South Korean men but not in women: The 2008–2010 Korean National Health and Nutrition Examination Survey

Table 2	Comparison of BMD	between subjects with and	without metabolic syndrome
		-	-

Skeletal site	Men			Premenopausal women			Postmenopausal women		
	MS ^a (+)	MS ^a (-)	р	MS ^a (+)	MS ^a (–)	р	MS ^a (+)	MS ^a (-)	p
LS BMD	0.970±0.002	0.989 ± 0.004	< 0.001	0.977±0.002	1.037±0.006	< 0.001	0.806±0.005	0.813±0.004	0.264
Adjusted ^b	0.967 ± 0.004	0.969 ± 0.003	0.658	0.980 ± 0.008	0.984 ± 0.004	0.602	0.800 ± 0.006	0.788 ± 0.006	0.056
TH BMD	0.978 ± 0.003	0.989 ± 0.004	0.007	0.893 ± 0.002	0.965 ± 0.006	< 0.001	0.782 ± 0.004	0.773 ± 0.004	0.078
Adjusted ^b	0.962 ± 0.004	0.971 ± 0.003	0.030	0.903 ± 0.007	0.904 ± 0.004	0.973	0.762 ± 0.005	0.759 ± 0.005	0.428
FN BMD	0.834±0.003	0.818 ± 0.004	< 0.001	0.761±0.002	0.808 ± 0.005	< 0.001	0.635 ± 0.004	0.620±0.003	0.001
Adjusted ^b	0.801 ± 0.004	0.814 ± 0.003	< 0.001	0.764 ± 0.007	0.764 ± 0.004	0.999	0.615 ± 0.004	0.613 ± 0.005	0.555

Data are presented as mean±SE of the population. P values were obtained by ANCOVA

BMD bone mineral density, LS lumbar spine, TH total hip, FN femur neck, MS metabolic syndrome

^a Data are defined as American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (AHA/NHLBI) criteria, in which the criteria for abdominal obesity were specified in an Asian population

^b Adjusted by age, BMI, smoking, alcohol use, and regular exercise

At any given BMI, men had higher visceral fat compared to women, so they are more susceptible to the adverse effects of MetS.



Relationship between metabolic syndrome and bone fracture

Features of the metabolic syndrome and the risk of non-vertebral fractures: The Tromsø study

Population- based, 6-year follow-up of 27,159 subjects from the municipality of Tromsø, followed from 1994 until 2001. Age range was 25–98 years.



- > Increasing number of metabolic syndrome features was associated with significantly reduced fracture risk in both men and women.
- High BP was protective against fracture in men
- Increased body mass index (BMI) was protective in women



Relationship between metabolic syndrome and bone fracture

Association between metabolic syndrome and bone fractures: a meta-analysis of observational studies





Relationship between metabolic syndrome and bone fracture

The Association between Metabolic Syndrome, Bone Mineral Density, Hip Bone Geometry and Fracture Risk: The Rotterdam Study

	Women			Men	
	All Fractures (371)			All Fractures (147)	
Metabolic Syndrome	Hazard ratio (95%CI)	P-value	Metabolic Syndrome	Hazard ratio (95%CI)	P-value
Model 1	0.85 (0.69-1.04)	0.12	Model 1	0.85 (0.60-1.20)	0.36
Model 2	0.91 (0.72-1.14)	0.40	Model 2	0.74 (0.69-1.08)	0.12
Model 3	0.91 (0.73-1.15)	0.43	Model 3	0.68 (0.46-1.006)	0.054
No. of MS components			No. of MS components		
Model 1	0.94 (0.87-1.02)	0.11	Model 1	0.92 (0.81-1.06)	0.24
Model 2	0.97 (0.89-1.05)	0.44	Model 2	0.86 (0.74-1.001)	0.055
Model 3	0.97 (0.89-1.06)	0.47	Model 3	0.82 (0.70-0.9964)	0.015
Non-V	Vertebral Fractures (307)		Non-1	/ertebral Fractures (102)	
Metabolic Syndrome	Hazard ratio (95%CI)	P-value	Metabolic Syndrome	Hazard ratio (95%CI)	P-value
Model 1	0.90 (0.72-1.13)	0.36	Model 1	0.89 (0.59-1.35)	0.59
Model 2	0.94 (0.73-1.21)	0.63	Model 2	0.69 (0.55-1.88)	0.12
Model 3	0.94 (0.73-1.21)	0.61	Model 3	0.64 (0.40-1.03)	0.068
No. of MS components			No. of MS components		
Model 1	0.96 (0.89-1.05)	0.38	Model 1	0.94 (0.79-1.10)	0.42
Model 2	0.98 (0.89-1.08)	0.70	Model 2	0.83 (0.68-1.01)	0.047
Model 3	0.98 (0.89-1.08)	0.66	Model 3	0.75 (0.66-0.96)	0.017
Ve	rtebral Fractures (123)		Ve	ertebral Fractures (62)	
Metabolic Syndrome	Hazard ratio (95%CI)	P-value	Metabolic Syndrome	Hazard ratio (95%CI)	P-value
Model 1	0.68 (0.47-0.98)	0.039	Model 1	0.65 (0.37-1.13)	0.13
Model 2	0.80 (0.53-1.19)	0.27	Model 2	0.67 (0.49-1.25)	0.20
Model 3	0.83 (0.56-1.24)	0.36	Model 3	0.60 (0.32-1.14)	0.12
No. of MS components			No. of MS components		
Model 1	0.84 (0.73-0.96)	0.01	Model 1	0.84 (0.6-1.03)	0.10
Model 2	0.86 (0.76-1.03)	0.11	Model 2	0.85 (0.75-1.07)	0.17
Model 3	0.90 (0.77-1.05)	0.18	Model 3	0.81 (0.64-1.03)	0.09

"()", number of fractures

Model 1: Adjusted for age

Model 2: Model 1 + Height and Weight

Model 3: Model 2 + smoking status, physical activity, alcohol intake, fallings in the last 12 months, use of diuretics drugs, use of hormone replacement therapy, use of corticosteroids drugs, use of drugs for bone and other musculoskeletal diseases and Dutch Healthy Diet Index.



Effects of Metabolic syndrome treatment on bone

STATINS: suppress the mevalonate pathway by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA reductase, thereby reducing prenylation of GTPases, which **favours bone formation**.

ANTIDIABETIC DRUGS:

1)Biguanides, insulin, sulfonylureas, glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase-4 (DPP-4) inhibitors promote osteoblast differentiation
2)sodium-glucose co-transporter 2 inhibitors and thiazolidinedione enhance bone loss
3)Increased association with hypoglycaemia, which contributes to increased fracture risk

ANTI HYPERTENSION DRUGS: thiazide diuretics and beta-blockers are associated with a small benefit in fracture risk reduction

Effects of Metabolic syndrome treatment on bone: weight reduction

Figure 3. Effect of Severe vs Moderate Energy Restriction on Body Composition in Postmenopausal Women With Obesity



Original Investigation | Nutrition, Obesity, and Exercise Effect of Weight Loss via Severe vs Moderate Energy Restriction on Lean Mass and Body Composition Among Postmenopausal Women With Obesity The TEMPO Diet Randomized Clinical Trial

Seimon RV, 2019





Effects of Metabolic syndrome treatment on bone: weight reduction





Effects of Metabolic syndrome treatment on bone: weight reduction by bariatric surgery

Bariatric surgery might be associated with increased PTH, bone turnover and reduced circulating calcium level and BMD
Mean Difference
Mean Difference



Bariatric surgery increased the risk of total and non-vertebral fractures, especially of the upper arms



Deficiency of nutrients, such as protein, folate, vitamin B6, B12 and trace elements may have detrimental effects on bone.



Effects of Bisphosphonate Treatment on Circulating Lipid and Glucose Levels in Patients with Metabolic Bone Disorders

		PDB-Zot			PDB-Clo			Op-Zol		
		TO	Tl	T6	то	T1	T6	TO	T1	T6
	Crea (µmol/l)	79.6±31.3	81.1±32.1	80.3±31.2	80.9±29.2	82.9±30.3	79.6±30.1	80.9±30.6	82.1±31.2	79.9±29.9
>	Glu (mmol/l)	5.19 ± 0.58	4.98±0.54*	4.91±0.52*	5.23 ± 0.52	5.41 ± 0.51	5.27 ±0.54	5.25 ± 0.51	4.97±0.51*	4.90 ± 0.49
	tCa (mmol/l)	2.37 ± 0.13	2.29 ± 0.12	2.32 ± 0.12	2.41 ± 0.14	2.29 ± 0.13	2.40 ± 0.13	2.34 ± 0.13	2.21 ± 0.12	2.32 ± 0.13
>	t-chol (mmol/l)	5.10 ± 1.06	$4.89 \pm 1.02^{*}$	4.71±1.01*	5.29 ± 0.99	5.18 ± 1.06	5.23 ± 1.05	5.09 ± 1.02	$4.86 \pm 1.05^{*}$	4.72 ± 1.03
	HDL-chol (mmol/l)	1.32 ± 0.41	1.31 ± 0.42	1.31 ± 0.43	1.49 ± 0.41	1.39 ± 0.42	1.39 ± 0.41	1.51±0.39	1.50 ± 0.41	1.50 ± 0.39
>	LDL-chol (mmol/l)	3.10 ± 0.96	2.98±0.89*	2.83±0.86 ^a	3.10 ± 0.83	3.11 ± 0.82	3.16 ± 0.85	2.92 ± 0.81	2.76±0.82 ^a	2.66 ± 0.79
>	TG (mmol/l)	1.49 ± 0.80	1.32 ± 0.82	$1.25 \pm 0.81^{*}$	1.53 ± 0.86	1.48 ± 0.82	1.50 ± 0.81	1.46 ± 0.78	1.31 ± 0.80	1.24 ± 0.80
	25OHD (nmol/l)	84.3 ± 18.7	82.4 ± 19.1	83.7±17.8	89.1 ± 18.4	88.4±18.1	87.1±17.2	85.1±17.6	83.4±17.8	81.6±16.9
	ALP (%)	155 ± 90^{b}	87 ± 32^{a}	78±27*	148 ± 84^{b}	114 ± 58^{a}	83±36*	75±22	67±21	65±26



Iannuzzo G, 2021



Take home message

- The relationship between MetS and BMD is complex. After adjusting for the effects of mechanical loading exerted by BMI, the association seems to be negligible. In addition, the relationship may be mediated by sex.
- The improvements of metabolic profile, glycaemic status, lipid profile and blood pressure will lead to reduced inflammation and oxidative status of the patients and benefit their bone health.
- Excessive weight loss due to MetS management could be detrimental to the bone, and exercises can balance it. In particular, the combination of calorie restriction and exercise can promote a reduction in fat mass while retaining lean and bone mass
- Proper management of MetS can benefit not only the cardiovascular system but also the skeletal system.