Società Medico Chirurgica di Ferrara

dal 1846

OSTEONECROSI DELLE OSSA MASCELLARI CORRELATA A FARMACI (MRONJ): UNA NECESSARIA GESTIONE MULTIDISCIPLINARE

Sabato 9 marzo 2024

MRONJ e diabete

Lupo Sabrina

Università degli Studi di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
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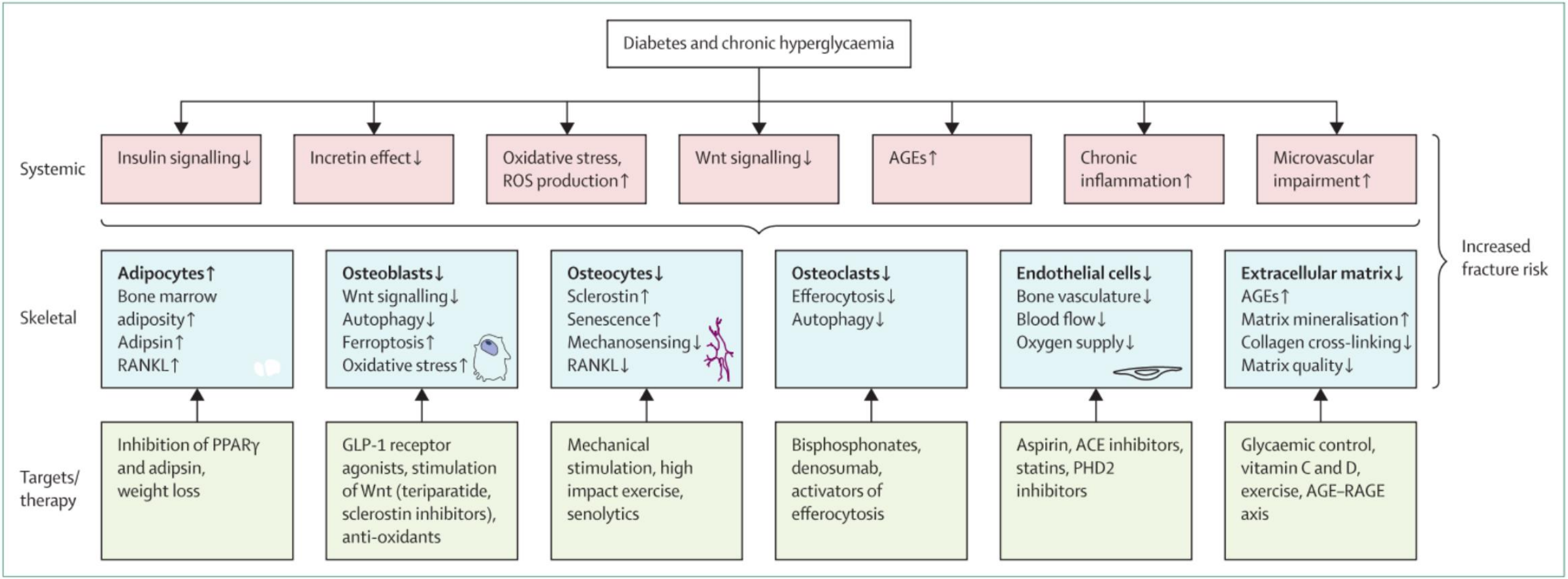
Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

FATTORI DI RISCHIO FARMACO-RELATI, SISTEMICI E LOCALI PER MRONJ

Risk Factor		
Drug-Related	**Systemic**	**Local**
Product (Antiresorptive/antiangiogenic drug) Route of administration (po, sc, iv, im) Cumulative dosage Duration of treatments Supportive care (e.g., chemotherapy, steroids, thalidomide)	Underlying disease (solid tumors, multiple myeloma, osteoporosis) Comorbidity (e.g., diabetes, rheumatoid arthritis, hypocalcemia, hyperparathyroidism) Lifestyle (e.g., smoking)	Dental/periodontal infection Peri-implantitis Oral surgeries (e.g., dental extractions) Unfitting removable dentures Anatomical conditions (e.g., torus, exostosis, pronounced mylohyoid ridge)

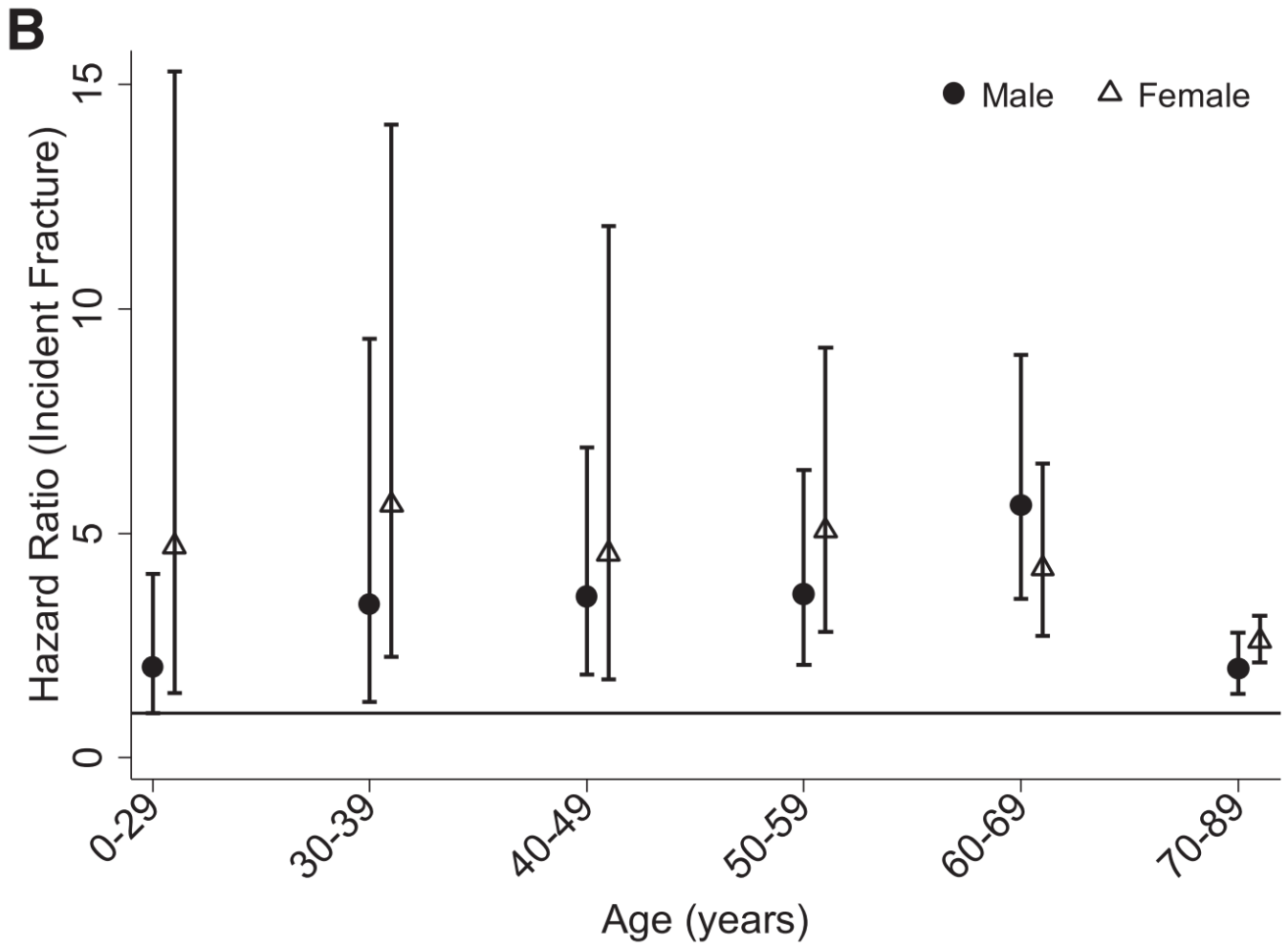
Campisi, G et al, *International journal of environmental research and public health*, (2020).

DIABETE MELLITO E FRAGILITA' OSSEA



Hofbauer et al, The lancet. Diabetes & endocrinology. (2022)

DIABETE MELLITO TIPO1 E RISCHIO DI FRATTURE

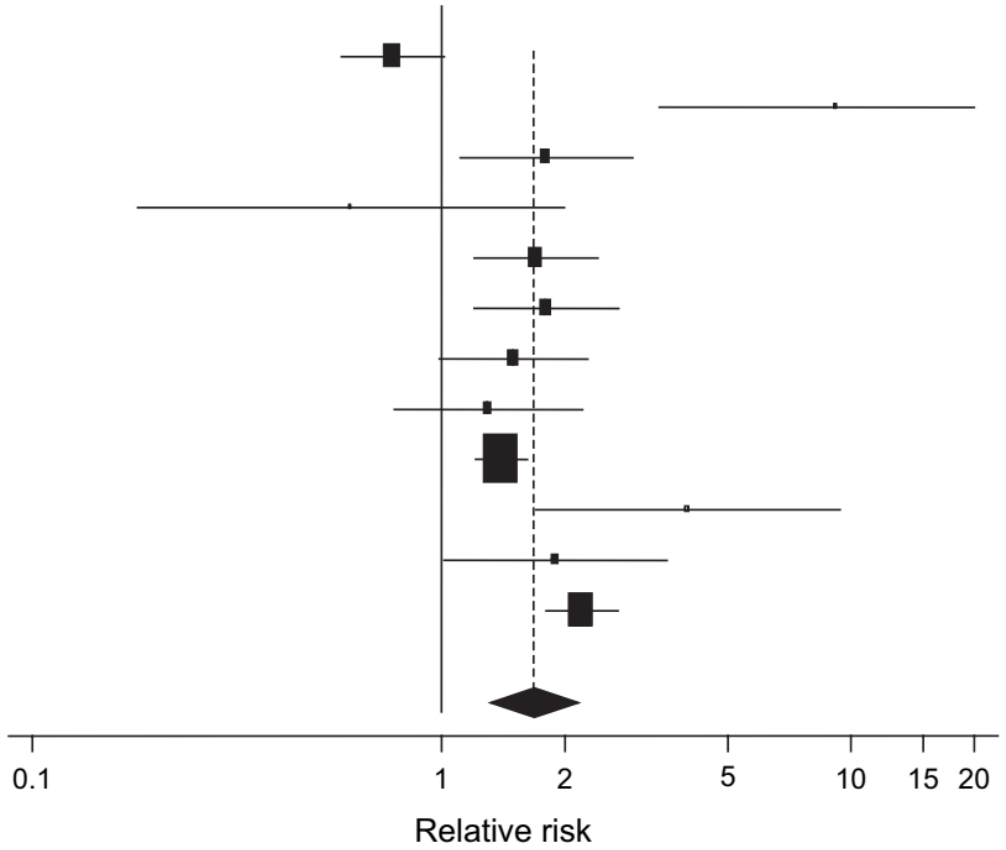


Weber, D. R. et al. Diabetes care. (2015)

DIABETE MELLITO TIPO2 E RISCHIO DI FRATTURE

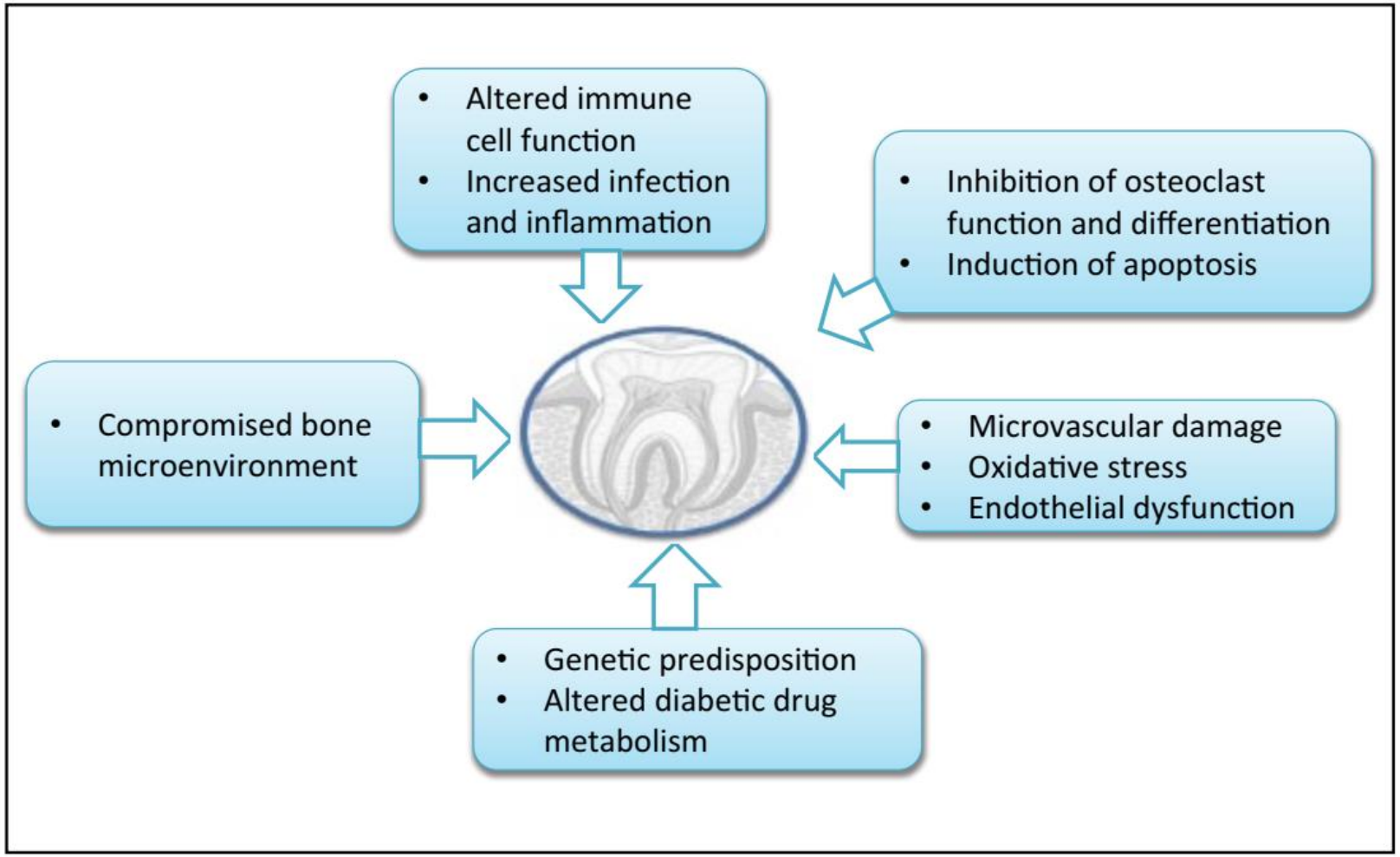
Study	RR (95% CI)
Heath et al., 1980 (15)	0.8 (0.6, 1.02)
Meyer et al., 1993 (25)	9.2 (3.4, 24.9)
Forsen et al., 1999 (14)	1.8 (1.1, 2.9)
Ivers et al., 2001 (8)	0.6 (0.2, 2.2)
Nicodemus and Folsom, 2001 (9)	1.7 (1.2, 2.4)
Schwartz et al., 2001 (12)	1.8 (1.2, 2.7)
Ottenbacher et al., 2002 (23)	1.5 (1.0, 2.3)
de Liefde et al., 2005 (29)	1.3 (0.8, 2.3)
Vestergaard et al., 2005 (20)	1.4 (1.2, 1.6)
Holmberg et al., 2006 (30)	4.0 (1.7, 9.4)
Ahmed et al., 2006 (28)	1.9 (1.02, 3.5)
Janghorbani et al., 2006 (21)	2.2 (1.8, 2.7)
All studies	1.7 (1.3, 2.2)

Test for heterogeneity:
$Q = 58.1$; $p < 0.001$



Janghorbani et al. American journal of epidemiology (2007)

DIABETE MELLITO E MRONJ: MECCANISMI PATOGENETICI

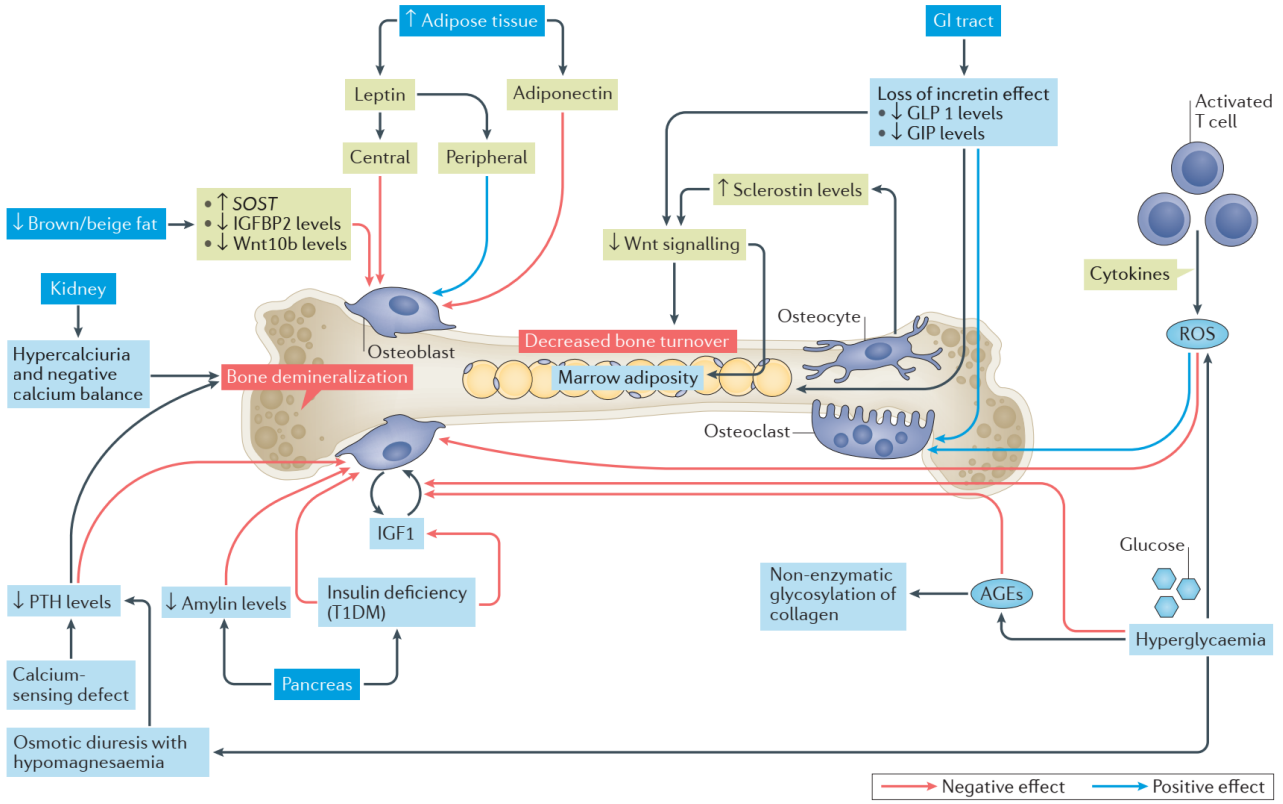


Peer, A et al, Journal of dental research, (2015).

MECCANISMI PATOGENETICI

RIDUZIONE DEL TURNOVER OSSEO E DEL REMODELING

- Changes in insulin levels
- Elevated levels of advanced glycation end products (AGEs) in collagen
- Increased urinary excretion coupled with lower intestinal absorption of calcium
- Inappropriate homeostatic response of parathyroid hormone secretion
- Complex alterations of vitamin D regulation
- Reduced renal function
- Lower insulin-like growth factor-1 (IGF-1)
- Microangiopathy
- Inflammation
- Thiazolidinedione treatment negatively affecting the bone



Napoli N et al, Nature reviews. Endocrinology (2017)
Peer, A et al, Journal of dental research, (2015).

MECCANISMI PATOGENETICI

AUMENTATA APOPTOSI DI OSTEOBLASTI E OSTEOCITI

- AGEs induce disruption in the osteoblastic actin cytoskeleton and alterations in cell morphology; the subsequent decrease in cell-substratum interactions was shown to increase apoptosis of osteoblasts and decrease osteoblastic proliferation
- RAGE appears to play a central role in oral infection, exaggerated inflammatory host responses, and the destruction of alveolar bone in DM

ALTERATA RISPOSTA IMMUNITARIA

- Diabetes induces changes in neutrophil, monocyte, and macrophage function
- Neutrophil adherence, chemotaxis, and phagocytosis are often impaired
- Conversely, the monocyte-macrophage cell line may be hyperresponsive to bacterial antigens, resulting in significantly increased production of proinflammatory cytokines
- Elevated levels of monocyte chemoattractant protein-1 (MCP-1) in gingival tissues, increased gingival inflammatory cell infiltration, and alveolar bone loss were reported in rats with either DM or periodontitis

Gangoiti MV et al, Acta Histochem (2013)

Peer, A et al, Journal of dental research (2015)

MECCANISMI PATOGENETICI

AUMENTO DELL'INFIAMMAZIONE

- Periodontal disease is the most prevalent oral complication of T2DM; T2DM confers a 2.81 increased risk of destructive periodontitis
- Decreased metabolic control in T2DM negatively affects all clinical measures of periodontal health and disease severity
- A bidirectional relationship between DM and periodontitis seems very likely; periodontal diseases can aggravate insulin resistance and adversely affect glycemic control, and periodontal treatment improves glycemic control in T2DM
- Activated T and B cells in the gingival tissues are the primary sources of RANKL, which induces osteoclastogenesis, osteoclast activation, and bone loss in periodontitis
- Inhibiting the function of RANKL produced by activated T cells can prevent alveolar bone loss
- Elevated levels of high-sensitivity C-reactive protein in gingival crevicular fluid were recently reported in T2DM patients with chronic periodontitis
- Interleukin (IL)–6 and the RANK/osteoprotegerin ratio were higher in the oral mucosa of patients with jaw necrosis than in those without

Peer, A et al, Journal of dental research, (2015)

MECCANISMI PATOGENETICI

DANNO MICROVASCOLARE E DISFUNZIONE ENDOTELIALE

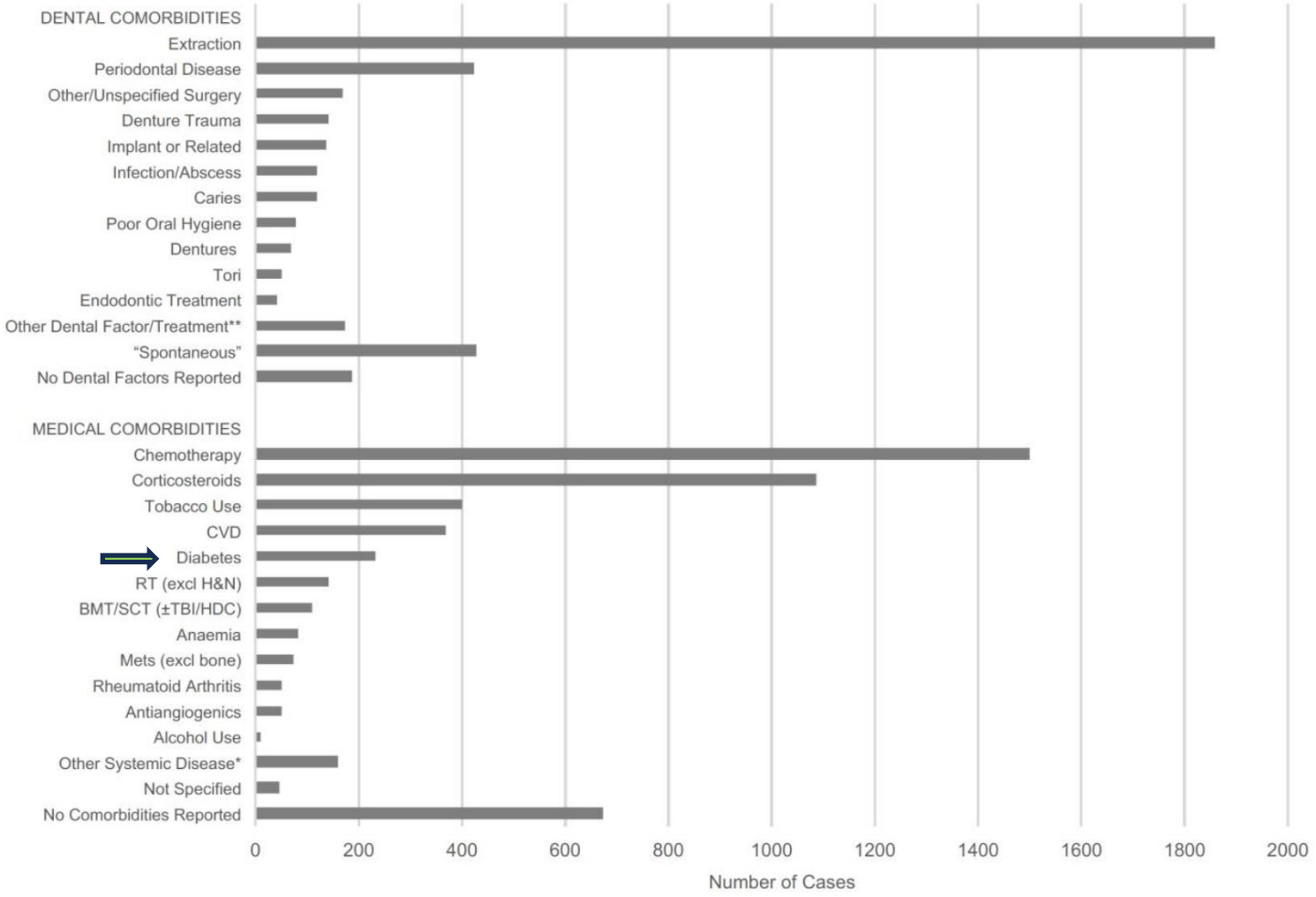
- DM-associated macrovascular and microvascular disease
- DM-related bone microvascular ischemia
- Increased oxidative damage
- Accelerated endothelial proliferation, resulting in poor functioning of blood vessels
- Decreased endothelial VEGF expression and endothelial function

FATTORI GENETICI

- DM genetic predisposition related to the *CYP 450* isoenzyme family
- Genetic polymorphisms affecting drug metabolism, excretion, and drug targets within pathways of bone metabolism and wound healing

Peer, A et al, Journal of dental research, (2015)

Risk factors for medication-related osteonecrosis of the jaws: A systematic review



McGowan, K et al. Oral diseases (2018)

MRONJ e DIABETE: DATI CLINICI

Table 2. Studies published concerning the relationship between diabetes and MR-ONJ. Where BP-ONJ refers to bisphosphonate-associated osteonecrosis of the jaws.

Study	Country	No. of Patients	Prevalence of Diabetes (%)	*p*-Value	Average Age	Comment
Vidal-Real, 2015 [19]	Spain	194	86.6	0.048	68.91	only patients treated with zoledronic acid; comparison BP-ONJ and BP-Treatment
Khamaisi, 2007 [18]	Israel	31	58	0.001	64.8	comparison BP-ONJ and BP-Treatment
Bocanegra-Perez, 2012 [22]	Spain	44	35	not calculated	64.2	
Fede, 2013 [26]	Italy	87	9.2	not significant	70.7	osteoporotic non-cancer patients
Anavi-Lev, 2013 [20]	Israel	52	41 *	0.02	74.5	comparison between iv and po BP-treatment; diabetes prevalence higher in po-group
Diniz-Freitas, 2012 [23]	Spain	20	20	not calculated	71.2	
Lazarovici, 2009 [24]	Israel	101	16	not calculated	63.5	
Watters, 2013 [21]	USA	154	24	0.05	64	only BP-ONJ-patients included, comparison between progressive disease and remission
Manfredi, 2011 [25]	Italy	25	16	not calculated	70.4	only patients with BP-treatment due to osteoporosis
Wilkinson, 2007 [29]	USA	16073	6.40	not significant	n/a	
Molcho, 2013 [27]	Israel	46	37	not significant	66	
present study, 2016	Germany	35	14.30	not significant	68.8	
			30.29		67.91	

* value recalculated.

Values	Control Group	MR-ONJ	*p*-Value
n	1339	35	
Age mean	47.53	64.94	$p < 0.001$
Age min	0	45	
Age Max	99	88	
Age standard deviation	23.85	8.37	
Known diabetes (%)	115 (8.6)	5 (14.3)	$p = 0.223$
Diabetes therapy			
Dietary (%)	31 (27.0)	0	
Medicinal (%)	84 (73.0)	5 (100.00)	
Nephropathy (%)	33 (28.7)	3 (60.0)	
Increased Creatinine level (%)	14 (12.1)	0	
Neuropathy	17 (14.8)	0	
Retinopathy	5 (4.3)	1 (20.0)	
Diabetic foot ulcer	4 (3.5)	0	
Gangrene	1 (0.9)	0	
Metformin	29 (25.2)	2 (40.0)	
Glinide	0	0	
Acarbose	0	0	
Sulfonylurea	14 (12.1)	1 (20.0)	
Glitazone	0	0	
Gliptin	4 (3.5)	0	
Insulin	38 (33.0)	2 (40.0)	
Average maximum blood glucose level (mg/dL)	105	113	
Number of patients with glucose values above 200 mg/dL (%)	142 (11.4)	10 (28.5)	$p < 0.001$
Number of diabetics (%)	80 (56.3)	4 (40)	

Hyperglycemia as a possible indicator for poorly managed or yet undetected diabetes is associated with MR-ONJ

Rahimi-Nedjat et al, Dentistry journal (2016)

Journal of
Clinical Medicine

MDPI

Article

Association between Hyperglycemia and Medication-Related Osteonecrosis of the Jaw (MRONJ)

Abstract: Background: Medication-related osteonecrosis of the jaw (MRONJ) is a type of jawbone necrosis caused by the use of drugs for some types of cancer and osteoporosis. The current study aimed to evaluate the associations between hyperglycemia and the development of medication-related osteonecrosis of the jaw. Methods: Our research group investigated data collected between 1 January 2019 and 31 December 2020. A total of 260 patients were selected from the Inpatient Care Unit, Department of Oromaxillofacial Surgery and Stomatology, Semmelweis University. Fasting glucose data were used and included in the study. Results: Approximately 40% of the necrosis group and 21% of the control group presented with hyperglycemia. There was a significant association between hyperglycemia and MRONJ ($p < 0.05$, $p = 0.003$). Vascular anomaly and immune dysfunction caused by hyperglycemia can lead to necrosis after tooth extraction. Necrosis is more common in the mandible (75.0%) and in the case of parenteral antiresorptive treatment (intravenous Zoledronate and subcutaneous Denosumab). Hyperglycemia is a more relevant risk factor than bad oral habits (26.7%). Conclusions: Ischemia is a complication of abnormal glucose levels, a possible risk factor for necrosis development. Hence, uncontrolled or poorly regulated plasma glucose levels can significantly increase the risk of jawbone necrosis after invasive dental or oral surgical interventions.

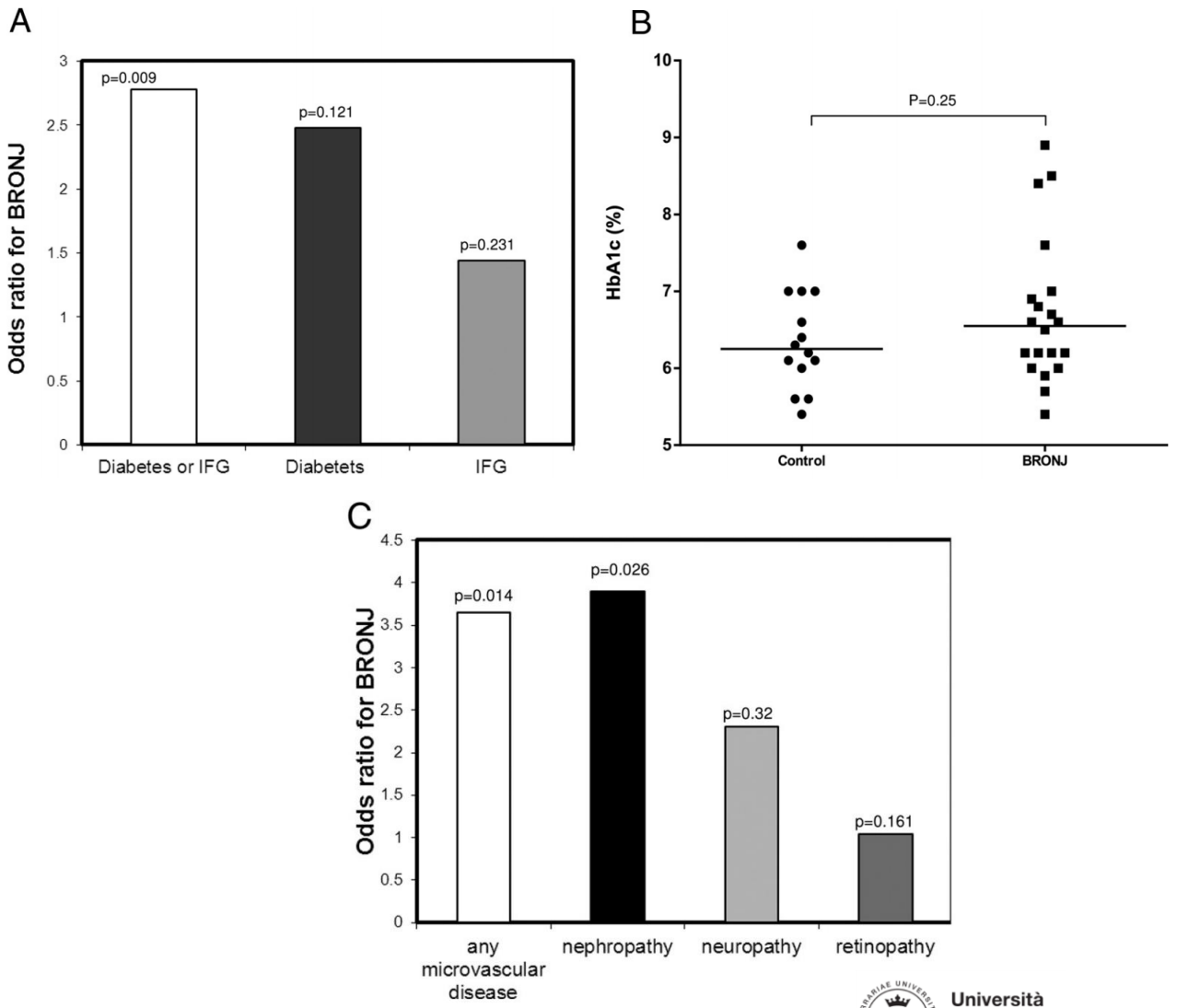
Diabetes Microvascular Disease and the Risk for bisphosphonate-related Osteonecrosis of the Jaw: A Single Center Study

Study group of 46 patients treated with bisphosphonates who were diagnosed with BRONJ

vs

Control group of 38 patients treated with bisphosphonates without evidence of BRONJ

- 67.4% of patients in study group had diabetes or impaired fasting glucose
- The proportion with diabetes (37%) was higher than in the control group (26.3%; P .009)
- The presence of diabetes or impaired fasting glucose increased the association with BRONJ by 2.78-fold (confidence interval 1.27– 6.07, *P* .009).
- The prevalence of microvascular disease was significantly higher in the BRONJ than in the control group (*P* .01).
- The presence of diabetic nephropathy increased the association with BRONJ by 3.9-fold



Molcho, S. Et al, The Journal of clinical endocrinology and metabolism. (2013)

CONCLUSIONI

Il diabete mellito potrebbe essere un fattore predisponente allo sviluppo di MRONJ a causa di diversi meccanismi patogenetici (riduzione del turnover osseo e del remodeling, aumentata apoptosi di osteoblasti ed osteociti, aumentata risposta infiammatoria, alterata risposta immunitaria, danno microvascolare e disfunzione endoteliale, fattori genetici)

L'attuale livello di evidenza scientifica in merito alla possibile relazione tra diabete mellito (DM) e ONJ farmaco-relata è ancora indefinito e
non consente di indicare un rapporto di chiara causalità-effetto

L'iperglicemia e la presenza di complicanze microvascolari potrebbero essere fattori di rischio associati alla MRONJ

Il paziente diabetico è un paziente ad elevato rischio fratturativo pertanto nella scelta terapeutica bisogna sempre valutare attentamente il rapporto rischio (ONJ)/beneficio

Grazie per l’attenzione!