Supplementary material

Supplementary Table i. Studies showing individual results of Sr effect on bone formation and/or bone remodelling. Results are presented according to the content of Sr used in the biomaterial and the average time from implantation to evaluation

ID	Strontium content	Time	Results
Bose[19]	1 wt%	4 wks	Increased bone formation in E *versus* C
		8 wks	Increased bone formation in E *versus* C
		12 wks	Presence of bone remodelling in E *versus* no bone remodelling in C
		16 wks	Bone remodelling with compact interface bone-implant in E *versus* fibrous interface in C
Tian[31]	1 wt%	4 wks	Similar observation of new bone in the margins of the implant, with no new bone formation in the centre in E and C. Increased number of osteoblasts (measurement of active bone formation) and presence of woven type of new bone in E *versus* C
		12 wks	Increased newly formed bone in E *versus* C; Presence of active osteoblasts in E and numerous osteoblasts in C; Presence of degradation of the scaffold in E
		16 wks	Presence of new bone regenerated and penetrated through the interconnective pores in E *versus* no new bone and only fibrous tissue in the centre of the scaffolds and increased quantity and density of the defected area in C
		Overall	Significantly increased percentage of new bone volume in E; Similar degradability and degradation rate in E and C Radiograph: Illegible bone boundary with implant in E and C
Xie[33]	2 wt%	4 wks	Increased bone volume in E *versus* C; Clearly visible interfaces of all the scaffolds in E and C
		8 wks	Increased bone volume in E *versus* C; Presence of new bone formation in the centre and similar degradation in E and C
		12 wks	Increased bone volume in E *versus* C; Large new bone in the centre of scaffolds with trabecular structure encasing the scaffold in E *versus* new bone regenerated and penetrated through the interconnective pores to the margin in C
Dagang[24]	5 wt%	4/8/12/24 wks	Higher degradability and mature bone (measured by haversian canals) in E *versus* C; similar/no inflammation reaction, no fibrous membrane on the interface, slight surface absorption in E and C. No significant differences in newly formed bone.
	10 wt%		Higher degradability, mature bone (measured by haversian canals) and surface absorption (obvious absorption pores) in E *versus* C; similar no inflammation reaction, no fibrous membrane on the interface in E and C. No significant differences in newly formed bone. Sr 10% *versus* Sr 5%: higher degradation and higher absorption pores
Gorustovich[25]	6 wt%	30 days	Similar affinity index (direct contact area), no fibrous layer, no macrophage and no inflammatory cells in the interface in E and C; EDX analysis with similar bond to bone through a calcium-phosphorus interface in E and C
Gu[26]	11.5 Ca/Sr MR	4 wks	Newly formed bone within and surrounding all the scaffolds in E *versus* only around the scaffolds in C
		8 wks	Presence of woven bone in E
		16 wks	Similar repair of most of the defect in E and C; greater ratio of newly formed bone/residual materials in E *versus* C
		Overall	Superior osteogenic capacity in E; Scaffold/bone boundary became illegible in E
Banarjee[18]	0.25/1 wt%	4 to 16 wks	Presence of new bone on the pre-existing cortical bone and on the implant in E *versus* only on the pre-existing cortical bone in C
Li[28]	5 wt%	4 wks	Immature bone trabeculae and cancellous bone in E *versus* original repair in the defect area in C. Radiograph: presence of reabsorption in experimental and control
		8 wks	Well organised mature bone trabeculae in E *versus* immature bone trabeculae in C
		12 wks	Complete cortical repair in E *versus* cortical bone tissue with many voids in C. Radiograph: implant was not noted radiographically and the cortex closed in E and C; Slower resorption rates and more compact bone repair in E *versus* C
	10 wt%	4 wks	Well differentiated bone trabeculae in E *versus* original repair in the defect area in C. Radiograph: Presence of reabsorption in E and C
		8 wks	Regeneration of incomplete cortical surface at the same level of the adjacent cortical plate in E *versus* immature bone trabeculae in C
		12 wks	Complete cortical repair in E *versus* cortical bone tissue with many voids in C. Radiograph: Implant was not noted radiographically and the cortex closed in E and C; Slower resorption rates and more compact bone repair in E *versus* C
	Overall	Overall	Micro-CT new bone formation and sporadic trabecular bone in the marrow canal in E and C; Improved new cortex formation in E *versus* C; significantly higher BMD and bone volume (relation BV/TV) in E *versus* C Sr 10% *versus* 5%: Non-significant difference in BMD and bone volume (relation BV/TV) in E *versus* C
Mohan[30]	1.67 (Ca+Sr)/P MR	4 wks	Significantly more newly formed bone in E *versus* C
		12 wks	Significantly more newly formed bone and material degradation in E *versus* C. Increased prominence of mature lamellar bone in E *versus* C
		Overall	Micro-CT: Increased bone volume, fraction trabecular number, trabecular thickness and bone density in E *versus* C
Zhao[35]	10 wt%	8 wks	Significantly higher mineralisation levels and new bone area in E *versus* C; Significantly lower material residual area in E *versus* C Micro-CT: Significantly superior bone volume (relation BV/TV), BMD and significantly higher blood vessel area and blood vessel number in E *versus* C
Izci[27]	NI	3/6/12 mths	Scintigraphy: Superior osteoblastic activity in E *versus* C. Micro-CT: Osseo-integration in E and C
Kang[38]	11.5 Ca/Sr MR	4 wks	Significantly more newly formed bone in E *versus* C
		12 wks	Significantly higher defect repair and newly formed bone in E *versus* C. Radiograph: significantly higher trapdoor cartilage and defect repair in E *versus* C

(Continued)

Supplementary Table i. (Continued)

ID	Strontium content	Time	Results
Tarafder[39]	1 wt%	4 wks	Significantly higher bone area fraction (total newly formed bone area/total area) and osteoid area fraction (osteoid area/total area) in E *versus* C
		8 wks	Significantly higher bone area fraction and osteoid area fraction in E *versus* C
		12 wks	Significantly higher bone area fraction in E *versus* C. Completely mineralised bone formation in E *versus* presence of osteoid in C
		16wks	Similar bone area fraction in E *versus* C
Tarafder[40]	1 wt%	8wks	Osteoid-like new bone formation E *versus* no osteoid-like new bone formation in C; Significantly higher bone area fraction (total newly formed bone area/total area) and osteoid area fraction (osteoid area/total area) in E *versus* C
		12wks	Significantly higher bone area fraction in E *versus* C; Significantly higher haversian canal area (haversian canal area/total area) in E *versus* C
Xie[41]	11.5 Ca/Sr MR	4 wks	Similar newly formed bone in E *versus* C; Similar new bone formation in the margins with no new bone in the centre of the implant in E and C; Higher degradability in E *versus* C
		8 wks	Higher newly formed bone in E *versus* C; Sporadic new bone formation in the centre of the implant in E *versus* no new bone in the centre in C
		12 wks	Higher newly formed bone in E *versus* C; Similar close union between implant and host bone in E and C; Trabecular bone in the centre of the implant in E *versus* only on the margins in C
Zhang[42]	9 mol% SrO	4/8 wks	Significantly higher bone-implant contact index in E *versus* C; Significantly lower Tb.Pf (Trabecular Bone Pattern Factor) in E *versus* C. Micro-CT: Significantly higher bone volume (relation BV/TV) in E *versus* C
Boyd[20]	0.14 SrO Mol Fract	4 wks	Mixed response of bone and fibrous tissue and no medullary inflammation in E and C
	0.28 SrO Mol Fract	4 wks	Presence of direct bone formation and no medullary inflammation in E
			Cortical healing in 3 of 6 of E and 2 of 6 of C; Similar bone marrow bone formation in E and C
Cardemil[21]	NI	6 days	Presence of local inflammatory reaction, with more new blood vessels and similar osteogenesis in E *versus* C
		28 days	Non-significantly higher proportion of bone at the centre of the defect in C *versus* significantly higher proportion of bone at the periphery of the defect in E; Significantly greater decrease in percentage of granule area in E *versus* C; less easily distinguished bone-granule interface in E; Bone formation in E and C
		6 days	Idem 6d
		28 days	Significantly higher proportion of bone at the centre of the defect in C *versus* significantly higher proportion of bone at the periphery of the defect in E; Significantly greater decrease in percentage of granule area in E *versus* C; less easily distinguished bone-granule interface in E; Bone formation in E and C Osteoporotic *versus* non-osteoporotic in E: trend to higher total-bone percentage; Significantly higher percentage of bone at the periphery
Wei[32]	5 wt%	2 wks	Similar new bone formation, presence of bone regeneration and woven trabecula in E and C
		4 wks	Significantly more new bone in E *versus* C
		8wks	Significantly more new bone, and superior bone thickness in E *versus* C
		Overall	Higher degradation rate and rate of new bone formed in E *versus* C Micro-CT: Increased bone volume fraction in E *versus* C Incorporation of Sr decreased significantly the number of osteoclasts;
Thormann[16]	0.123 Sr/Ca MR	6 wks	Statistically higher new bone formation in E (also increased fragmentation and osteoid formation) *versus* C; Significantly more bone formation at the bone-biomaterial interface region in E *versus* C; Significantly higher TRAP-positive cells in E *versus* C
Zhang[34]	2.5 wt%	2 wks	Similar percentage of bone regeneration in E and C; Micro-CT: Significantly superior bone volume (relation BV/TV), trabecular number and trabecular thickness and significantly inferior trabecular separation in E *versus* C
		4 wks	Significantly higher percentage of bone regeneration in E *versus* C; Presence of maturing trabecula forming lamellar bone with osteoclasts involving the bone remodelling in E *versus* dispersed or scattered newly formed bone in C. Micro-CT: Significantly superior bone volume (relation BV/TV), trabecular number and trabecular thickness and significantly inferior trabecular separation in E *versus* C
		8 wks	Significantly higher percentage of bone regeneration in E *versus* C; Greater amount and thickness of trabecula, with plenty of osteocytes clearly visible in the mineralised bone matrix in E *versus* C Micro-CT: Significantly superior bone volume (relation BV/TV), and trabecular thickness, similar trabecular number and trabecular separation in E *versus* C
	5 wt%	2 wks	Similar percentage of bone regeneration in E and C Micro-CT: Significantly superior bone volume (relation BV/TV), trabecular number and trabecular thickness and significantly inferior trabecular separation in E *versus* C Sr 5% *versus* Sr 2.5%: Similar percentage of bone regeneration; Micro-CT: Significantly superior bone volume (relation BV/TV), trabecular number and trabecular thickness, and significantly inferior trabecular separation in E *versus* C
		4 wks	Significantly higher percentage of bone regeneration in E *versus* C. Micro-CT: Significantly superior bone volume (relation BV/TV), trabecular number and trabecular thickness, and significantly inferior trabecular separation in E *versus* C Sr 5% *versus* Sr 2.5%: Micro-CT: Significantly superior bone volume (relation BV/TV), trabecular number and trabecular thickness, and significantly inferior trabecular separation in E *versus* C
		8 wks	Significantly higher percentage of bone regeneration in E *versus* C. Micro-CT: Significantly superior bone volume (relation BV/TV), and trabecular thickness, similar trabecular number and significantly inferior trabecular separation in E *versus* C. Sr 5% *versus* Sr 2.5%: Significantly higher percentage of bone regeneration; Micro-CT: Significantly superior bone volume (relation BV/TV) and trabecular thickness, similar trabecular number and trabecular separation in E *versus* C
Baier[15]	NI	1 mth	Similar circumferential contact index, ingrowth index, implant discontinuities and implant discontinuities containing newly formed bone in E and C

Supplementary Table i. (Continued)

ID	Strontium content	Time	Results
		3 mths	Significantly higher circumferential contact index, ingrowth index, implant discontinuities and implant discontinuities containing newly formed bone in E *versus* C
		6 mths	Non-significantly higher circumferential contact index in E *versus* C; Significantly higher ingrowth index, implant discontinuities and implant discontinuities containing newly formed bone in E *versus* C
Lin[29]	10 wt%	4 wks	Significantly higher mineralised tissue, newly formed bone and blood vessels in E *versus* C; Significantly lower remnant scaffold area in E *versus* C. Micro-CT: Increased newly formed bone area, significantly increased new bone mineral density, higher bone volume/total volume ratio and higher trabecular thickness in E *versus* C
Cheng[22]	CPC – 8.36 wt%	6 wks	PET scan: Significant increase in bone formation in the biomaterial-bone interface in E *versus* C; Non-significant differences in defect region in E *versus* C
	Xerogel – 20 wt%		PET scan: No significant differences in bone formation in E *versus* C
	Iron Foam – 22 wt%		PET scan: No significant differences in bone formation in E *versus* C
Cheng[23]	8.36 wt%	6 wks	PET scan: Increased bone formation in E *versus* C
Jebahi[36]	0.1 wt%	60 days	Similar presence of newly formed bone in E and C; Highly cellular layer, more advanced ossification and more bone regeneration in E *versus* sparser osteoid deposition in C
Jebahi[37]	0.1 wt%	90 days	Significantly superior bone volume (relation BV/TV), osteoblast number and Ob.S/BS in E *versus* C; Significantly lower Oc.S/BS and OV/BV in E *versus* C; Similar mineralising surface (MS/CS) in E and C; EDX analysis showed higher bioactivity in bone-implant surface E *versus* C

E, Experimental; C, Control; w, weeks; d, days; m, months; wt%, weight percentage; MR, Molar Ratio; Mol Fract, Molar Fraction; CT, Computed Tomography; PET, Positron-Emission Tomography; EDX, Energy-dispersive X-ray analysis; BMD, Bone Mineral Density; BV/TV, Bone Volume/Total Volume; Ob.S/BS, Osteoblast/Bone Surface; OV/BV, Osteoid/Bone Surface; Oc.S/BS, Osteoclast/Bone Surface; MS/CS, Mineralising Surface.

Where available, comparisons among study times or Sr doses are presented. Unless stated otherwise, results are from histology and/or histomorphometric analysis. Shaded cells represent results from osteoporotic models.

Supplementary Table ii.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1/2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2/Figure 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2/Figure 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2/Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2/Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2/3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2/5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8/Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-10/Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2/Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10/15/16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Prisma Statement Checklist.

N/A: Non-Applicable. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.