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2 Lifetime high calcium intake 3 increases osteoporotic fracture risk in old age

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Summary Caloric restriction prolongs life span. Calcium restriction may preserve bone health.

In osteoporosis, bone mineral density (BMD) has significantly decreased, due to a lack of osteoblast bone formation. Traditional osteoporosis prevention is aimed at maximizing BMD, but the lifetime effects of continuously maintaining a high BMD on eventual bone health in old age, have not been studied. Strikingly, in countries with a high mean BMD, fracture rates in the elderly are significantly higher than in countries with a low mean BMD. Studies show that this is not based on genetic differences. Also, in primary hyperparathyroidism, on the brink of osteoporosis, BMD levels may be significantly higher than normal.

Maybe, BMD does not represent long term bone health, but merely momentary bone strength. And maybe, maintaining a high BMD might actually wear out bone health.

Since osteoporosis particularly occurs in the elderly, and because in osteoporotic bone less osteoblasts are available, the underlying process may have to do with ageing of osteoblastic cells.

In healthy subjects, osteoblastic bone cells respond to the influx of calcium by composing a matrix upon which calcium precipitates. In the process of creating this matrix, 50–70% of the involved osteoblasts die. The greater the influx of calcium, the greater osteoblast activity, and the greater osteoblast apoptosis rate. An increased osteoblast apoptosis rate leads to a decrease in the age-related osteoblast replicative capacity (ARORC). In comparison to healthy bone, in osteoporotic bone the decrease in the replicative capacity of osteoblastic cells is greater. Due to the eventual resulting lack of osteoblast activity, micro-fractures cannot be repaired. Continuously maintaining a high BMD comes with continuously high bone remodeling rates, which regionally exhaust the ARORC, eventually leading to irreparable microfractures.

Regarding long time influences on bone health, adequate estrogen levels are known to be protective against osteoporosis. This is generally attributed to its inhibiting influence on osteoclast activity. Instead, its net effects on osteoblast metabolism may be the key to osteoporosis prevention. Adequate estrogen levels inhibit osteoblast activity, calcium apposition and osteoblast apoptosis rate, preserving the ARORC.

Conclusion: Regarding osteoporosis prevention, ARORC better than BMD represents bone health. Regarding ARORC, adequate estrogen levels are protective, opposing the similar effects of hyperparathyroidism and a high calcium diet.

Tests need to be performed in mice to assess the lifetime effects of a high versus a low calcium diet, on eventual bone fracture toughness.

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37 Introduction

38 Osteoporosis represents a major public health
39 problem. Efforts to prevent osteoporosis have not
40 been successful, which is demonstrated by in-
41 creased incidence of age-adjusted osteoporotic
42 fractures. For decades, prevention of osteoporosis
43 has been aimed at increasing peak bone mass, but
44 in countries with a high mean bone mineral density
45 (BMD), osteoporosis incidence is high as well.

46 In Europe, BMD of healthy female adults in Po-
47 land are lower than those in French, Italian and
48 Spanish populations [1]; and the age-adjusted inci-
49 dence of hip fractures is lower as well [2]. In Swe-
50 den, the mean BMD is higher [3], and so is hip
51 fracture incidence [2].

52 Japanese subjects have lower peak bone mass
53 than their European counterparts and also hip frac-
54 ture incidence is lower in Japan than in the West
55 [4]. This lower BMD is not due to genetic differ-
56 ences; US-born Japanese-American women have
57 BMD values equivalent to those of white normals
58 [5].

59 Women in China have lower BMD and much lower
60 risk of hip fracture than women in Europe or North
61 America [6]. This lower BMD is not due to genetic
62 differences; Chinese premenopausal women who
63 immigrated to Denmark more than 12 years ago
64 have a similar BMD to that of Danish premenopausal
65 women [7].

66 In Gambia, calcium intake, mean BMD and osteo-
67 porosis incidence are all very low [8]. Again, this
68 has no genetic cause. There are no significant dif-
69 ferences in BMD in Gambian and Caucasian adults
70 living in the UK [9].

71 Might maintaining a low BMD preserve long-term
72 bone health?

73 Maybe, BMD does not represent long term bone
74 health, but merely momentary bone strength.
75 And maybe, maintaining a high BMD might actually
76 wear out bone health, eventually causing poor
77 bone strength; in as much as constantly speeding
78 will cause your car to break down sooner.

79 Hypothesis: osteoporotic fractures result 80 of exhausted age-related osteoblast 81 replicative capacity (ARORC)

82 Caloric restriction elongates life span [10–13] by
83 retarding age-related physiological and biochemi-
84 cal changes [14–16]. Calcium restriction may pre-
85 serve bone-health by retarding the decrease in
86 the age-related osteoblast capacity to form new
87 bone.

The short-term effects of a high calcium intake
have been well established. In our bones, osteo-
blasts create the matrix upon which calcium pre-
cipitates. A high calcium intake leads to an
increased activity of osteoblasts and increased
bone formation rates, which, depending on bone
resorption rates, may increase BMD, and thus cre-
ate stronger bones.

In maintaining a higher BMD, both bone forma-
tion and bone resorption are increased. Unfortu-
nately, 50–70% of the composing osteoblasts die
in the composition of new matrix [17], and osteo-
blasts have a limited proliferative capacity [18–
20]. Increased osteoblast activity and cell differen-
tiation coincide with increased osteoblast apopto-
sis rate [21,22], which is specific for the
proliferating zone [21,23,24]. Increased osteoblast
apoptosis rates accelerate the decrease in the age-
related osteoblast replicative capacity (ARORC).

Osteoblasts from osteoporotic bone have a se-
verely reduced replicative capacity [25,26]. There-
fore, in osteoporotic bone, less osteoblasts are
available [27–29] and/or osteoblast activity is im-
paired [28–32], as in ‘exaggeratedly aged’ bones
[25,33]. Due to this lack of osteoblast activity, less
pre-calcified matrix is available [34] and micro-
fractures cannot be repaired [35].

In osteoporotic patients, there is no occurrence
of a generalized premature cellular aging [36]. In-
stead, the decrease in osteoblast activity is regio-
nal [27,28], indicating external factors, such as
the regional over-use of osteoblasts.

Similar to high-calcium diet, inadequate estrogen levels stimulate osteoblast activity and increase osteoblast apoptosis

It has been well-established that optimum estrogen
levels are protective against osteoporosis. This is
generally attributed to predominant inhibitory ef-
fects on bone resorption, but the influence of ade-
quate estrogen levels on osteoblast metabolism
may be key to understanding the etiology of
osteoporosis.

It has often been claimed that estrogen stimu-
lates osteoblast activity, but these findings may
have been the result of the previous use of inade-
quate methods. After verification and character-
ization of the reported anabolic effects of
estrogen on bone formation in growing rats, the
compiled data consistently demonstrated that
estrogen inhibits bone formation [37].

Other studies reported anabolic effects in the
first six days of estrogen administration [38] or
when added intermittently [39].

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141 On the longer haul, estrogen does not stimulate,
142 but suppresses osteoblastogenesis [40], attenuat-
143 ing osteoblast birth rate [41,42], inhibits human
144 osteoblast cell proliferation, differentiation and
145 activity [43–46], bone formation, [47–49] and pre-
146 vents osteoblast cell death [42,50,51], thereby
147 increasing osteoblast lifespan [40,42,52]. Partly,
148 estrogen may inhibit osteoblast activity by modify-
149 ing the effects of parathyroid hormone (PTH) [53].

150 More importantly, as osteoporosis is particularly
151 prevalent in postmenopausal women, estrogen
152 deficiency is responsible for increased osteoblasto-
153 genesis [54], increases the number of osteoblasts
154 [55] and osteoblast activity [56], accelerating bone
155 formation [49,54,57–61] (and predominantly bone
156 resorption), increasing osteoblast apoptosis rate
157 [62], shortening the lifespan of osteoblasts [63,64].

158 Regarding understanding the etiology of osteo-
159 porosis, the net effects of estrogen on BMD are
160 not the issue, because BMD only represents
161 momentary bone strength. Instead, the net effects
162 of adequate and inadequate estrogen levels on
163 osteoblast activity, apoptosis rate and the ARORC
164 are essential, explaining the possible detrimental
165 effects of a high calcium diet on eventual bone
166 health.

167 **Effects hyperparathyroidism on ARORC** 168 **similar to effects of high calcium intake**

169 Opposed to and inhibited by adequate estrogen lev-
170 els, prolonged hyperparathyroidism (HPTH) is a
171 well-known cause of osteoporosis, which is often
172 attributed to its stimulating effects on bone
173 resorption. Osteoblasts, however, are the main tar-
174 get cells for parathyroid hormone (PTH) [65]. Inter-
175 mittent and continuous PTH have similar effects on
176 the number of osteoblasts and bone-forming activ-
177 ity [66]. PTH stimulates osteoblast proliferation
178 [67–71], enhances osteoblast differentiation
179 [70,72,73], increases osteoblast number and min-
180 eral apposition rate [74,75], stimulating bone for-
181 mation [76–78]. PTH supplementation may
182 induce a net gain of bone mass [79,23,80–82], sim-
183 ilar to the effects of a high calcium diet.

184 In HPTH, bone formation (and resorption) rate is
185 markedly elevated [83] and increases in formative
186 and resorptive markers seem to be of equivalent
187 size [84]. Therefore, in HPTH, BMD values widely
188 differ [85], depending on the regional balances be-
189 tween increased osteoblast and osteoclast activity.
190 Some BMD values may be significantly higher than
191 in controls [86]. The resulting BMD values, how-
192 ever, are not the issue, because they only reflect
193 momentary bone strength. The issue is long-term

bone health, which is compromised by increased
osteoblast apoptosis rates.

PTH-induced osteoblast apoptosis is specific for
the proliferating zone [23,24], indicating that the
effects of PTH on apoptosis can only be explained
on the basis of its anabolic effect on osteoblast
proliferation, similar to the effects of a high cal-
cium diet.

HPTH eventually leads to exhaustion of the AR-
ORC, causing osteoporosis. HPTH enhances frac-
ture risk [87–89].

Regardless of the net effects on BMD, estrogen
inhibits, and a high calcium diet and HPTH increase
bone turnover. Regarding ARORC, estrogen is
therefore protective, opposing the effects of HPTH
and a high calcium diet.

Calcitriol may be preventive regarding osteoporosis due to its PTH-inhibiting effects

The protective or opposite effects of 1,25 dihy-
droxycholecalciferol (Calcitriol) on the ARORC
depend on coexisting PTH levels. Similar to PTH,
but to a lesser extent, Calcitriol directly stimulates
osteoblast differentiation and activity, increasing
osteoblast apoptosis [22], accelerating the de-
crease in the ARORC. Indirectly, however, Calci-
triol may be protective due to its inhibitory
effects on PTH levels, net downregulating both
osteoclast and osteoblast activity [90], which
attenuates the decrease in the ARORC.

Glucocorticoids cause osteoporosis due to direct pro-apoptotic effects

Long-term glucocorticoid therapy promptly induces
osteoporosis, whose severity depends on the dose
and duration of the treatment [91].

Glucocorticoids directly stimulate an increase in
the apoptosis of mature osteoblasts [92–94], un-
like the indirect effects of HPTH and a high calcium
diet, which increase osteoblast apoptosis by stimu-
lating osteoblast proliferation and activity.

Glucocorticoids decrease BMD by inhibiting
osteoblast activity, and simultaneously accelerate
the decrease of the ARORC by inducing osteoblast
apoptosis.

The limited influence of exercise indicates exhaustion of osteoblast replicative capacity

Exercise is positively associated with BMD of the
hip, but often osteoporosis patients cannot

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242 increase their BMD through exercise [95]. The possible exercise-induced bone mass gain is far less than the disuse-induced bone loss [96], which may indicate exhaustion of the ARORC.

246 Exercise is essential to maintain the shock-absorbing effects of strong muscles [97]. In the short-term, in older adults, exercise can partially (20–40%) decrease hip-fracture risk [98], but this will accelerate the decrease in the ARORC. In elderly women who had previously been diagnosed with hip fracture, a protective effect was found for women who were moderately active recently. In women, however, who were very active recently, hip fracture risk was slightly elevated [99], which might indicate a lack of osteoblast capacity to repair loading-induced microfractures. The later in life, the smaller the effects of exercise [100], due to the decrease in the ARORC. In elderly with a mean age of 73, exercise was not protective for osteoporotic fracture [101]. In women of about the same age, with a history of postmenopausal fractures, exercise did not affect BMD or fracture rates either [102].

265 Regarding osteoporotic fracture risk, exercise may have long-term beneficial effects by focusing on increasing muscle strength rather than bone strength.

269 Conclusion

270 Regarding osteoporosis, BMD represents momentary bone strength and ARORC represents long-term bone health. Regarding ARORC, adequate estrogen levels are protective, preserving osteoblast viability, opposing the pro-apoptotic effects on osteoblasts of glucocorticoid therapy, hyperparathyroidism and a high calcium diet. Maintaining a high BMD has adverse effects on long-term bone health, explaining the positive correlation between mean BMD and age adjusted osteoporotic fracture incidence, per country.

281 Osteoporosis prevention may be successful by aiming to reduce mean calcium intake to the level of countries where osteoporotic fracture incidence is lowest, approximately 300–500 mg/day.

285 Tests need to be performed in mice (half the population at 90% and the remaining at 100% of average life-expectancy) to assess the lifetime effects of a very high (3%), high (1.5%), moderate (0.5%), low (0.2%) and very low calcium diet (0.1%) respectively (Ca/P = 1.5, Ca/Mg = 10, Mg > 0.02%), on eventual bone fracture toughness.

292 More beneficial effects of exercise may be obtained by focusing on increasing muscle strength rather than bone strength.

If this theory is correct, worldwide millions of people may have been treated wrongly, and traditional prevention may have had, and will continue to have, strong adverse effects on the health of hundreds of millions of people. Even the most conservative estimates of costs are astronomical.

Acknowledgements

The first version of this theory was published at www.4.waisays.com in 2000. To obtain inspirational criticism, the theory was submitted to the online science forum of The Guardian, where M. Robert Showalter encouraged me to dig deeper in various directions, and to contact scientists specialized in all related fields.

In long fax-discussions, H.M. Frost (Southern Colorado Clinic) showed me how seemingly oppositional approaches may still be intertwined, confined by one common dogma. Not until 2004, Nobel Prize-winner for Physics in 1989, Prof. Hans Dehmelt, finally convinced me to submit my theory to Medical Hypotheses.

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