心血管疾病之骨質流失

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摘　要

傳統上，骨質疏鬆症和心血管疾病被認為是單獨的慢性疾病。現在越來越多的證據支持骨質疏鬆症與高血壓、血脂代謝異常、動脈粥樣硬化、血管鈣化和充血性心臟衰竭之間的直接關聯。近年來病理生理關係在骨質疏鬆症與心血管病的常見危險因素方面取得了重大進展。而這些共同的病理生理機制能如能進一步地理解，可能有助於未來對骨代謝和心血管疾病的治療方法。

關鍵詞：骨質疏鬆症(Osteoporosis)
心血管疾病(Cardiovascular disease)
動脈粥樣硬化(Atherosclerosis)

前　言

骨質疏鬆症是全身的骨骼疾病，其特徵是減少的骨礦物密度 (bone mineral density)，可導致骨骼脆弱和增加骨折機率[1]。因為盛行率在骨質疏鬆症、動脈粥樣硬化、高血壓、心血管疾病上都是隨著年齡而增長，這些條件可能會更頻繁地共存在現今老齡化社會[2]。傳統上，骨質疏鬆症與心血管病被認為是單獨的慢性疾病。兩者都會造成重大的致病率和死亡率的主要健康問題。現在越來越多的證據支持骨質疏鬆症和心血管疾病及年齡或常見心血管危險因素之間的直接關聯性[3-13]。

幾個回顧性分析呈現出低骨質密度與動脈粥樣硬化血管疾病之間，有年齡、吸煙、 糖尿病、或血脂代謝異常的重要關聯[5,6]。由Sennerby等一項研究的結果，有初始心血管疾病的診斷和一個隨後發生的髖部骨折的風險之間提出了顯著的關聯性[7]。此外，男性心肌梗塞的存活者中被報導具有低骨質密度[8]。再者，骨質疏鬆症和高血壓[14-16]、動脈粥樣硬化[17]、血管鈣化[18]和充血性心臟衰竭(CHF)[19]之間發現有顯著的相關性。一些心血管風險因素，如缺乏體力活動、吸煙、血脂代謝異常、糖尿病、高血壓、氧化壓力和發炎反應也與低骨質密度的發生率較高有關。

基於這樣的資料，本文的重點是回顧包括心血管疾病和骨質疏鬆症的病理生理機制，流行病學方面，常見的危險因素之間的關係和其相互作用。

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一、心血管疾病和骨質疏鬆症的常見風險因素

(一)高血壓

高血壓定義為收縮和舒張血壓值分別為高於 140 毫米汞柱和 90 毫米汞柱[20]。高血壓仍然是全世界死亡的主要原因，是世界上最大的公共衛生問題[21]。

流行病學研究顯示，血壓升高為心血管疾病的獨立預測因子[22]。高血壓和骨質疏鬆症均是多因素疾病，其中的遺傳因素和生活方式有助於啟動發病機制[23,24]。與增加血壓相關的因素包括年齡、缺乏身體活動、飲酒過量、攝取過多的鹽分。罹患骨質疏鬆症也有這些相同的危險因素[16]。

高血壓本身可能就是骨質疏鬆症的危險因素。然而，關於血壓高和骨質流失之間的關聯的現有證據尚不充分。在英國婦女的一項研究，Cappuccio等人發現股骨頸骨質密度的雙能量X射線吸收測定法(DEXA)檢測和收縮壓和舒張壓值呈負相關[25]。與此相反，Mussolino等使用資料來自美國國家健康和營養檢查調查(NHANES)報告分析，非裔美國人和白人中的男性或女性骨質密度與高血壓之間並沒有顯著的關聯性[26]。而之前的研究可以解釋這些矛盾可能原因是由不同的患者群體、診斷方法、或診斷標準的結果。最近,來自韓國的一項研究指出,股骨頸骨質密度與高血壓在中年以上人口(大於50歲)有顯著相關性[27]。

從一些動物實驗和臨床研究報告，高血壓與骨代謝相關的證據。與高血壓有關的鈣流失，可能是由於腎調節缺陷後導致鈣從骨質中移出，從而增加對骨質疏鬆症的風險。有幾項研究都一致指出，高血壓患者可能導致尿中鈣排泄量持續增加[16,28]。由原發性高血壓和正常腎功能的患者中研究鈣的代謝，發現高血壓病人增加鈣自腎臟中的流失[28,29]。這些結果支持原發性高血壓患者的鈣主要是由腎流失的論點。此外，高血壓與鈣代謝異常是導致增加鈣的流失，副甲狀腺代償性活化，增加鈣從骨的移出[25,30]。這種長期的鈣代謝異常，可能會構成高血壓性骨質流失的病理生理機制之一。不過也有一些研究指出，有高血壓的婦女，在停經之後，其骨質減少與血壓無關聯性[26,29]。

腎素-血管收縮素系統 (renin-angiotensin system, RAS) 是血壓調節的一個重要部分。一些流行病學研究報告指出，血管收縮素轉換酶抑制劑(ACEIs) 和血管收縮素受體阻斷劑（ARBs)在增加骨量和骨折的降低風險是有益處[31-35]。ACEIs 和ARBs的主要生理功能阻止血管收縮素II的生成。腎素-血管收縮素系統促使血管收縮素II合成中可能影響到骨代謝[31,32]。動物研究中發現骨質疏鬆症和血管收縮素II有牽連[34]，且人類的研究也發現血管收縮素II濃度增加的高血壓患者中，產生增加骨吸收和抑制骨礦化的有害影響[36,37]。血管收縮素II在高血壓有關的骨質疏鬆症扮演重要的作用，可能經由血管收縮素II接受體在成骨細胞和破骨細胞上的表現[33,34,38]。破骨細胞的分化主要是護骨素(OPG)和RANKL (receptor activator of nuclear factor κB ligand)系統所控制的[39-41]。而Cbfa1和RANKL是維持骨骼平衡的重要因素，也是調控成骨細胞和破骨細胞分化的重要關鍵，兩者都是受cAMP依賴性的訊息所調控。血管收縮素II負向調控Cbfa1的表現，但血管收縮素II正向調控RANKL表現。血管收縮素II通過改變cAMP依賴性途徑，來改變Cbfa1/RANKL呈現的比例，以此方式調節成骨細胞和破骨細胞的分化，進而導致增強骨吸收和減少骨形成[42]。

(二)脂質代謝及骨質疏鬆症

基於來自動物研究、實驗室分析、流行病學研究和臨床對照試驗中的證據，血脂代謝異常和心血管疾病之間明確的因果關係已經建立[43]。關於骨質疏鬆症和心血管疾病之間的密切關聯性，其共同致病的機制，一部分是骨質流失和脂質代謝異常之間的關係。血脂與骨質密度相關性的數據之間一直是不一致的。一些流行病學和實驗研究數據表示，血脂代謝異常可能和年齡相關的骨質疏鬆症具有重要的致病作用。骨質疏鬆症的骨質密度降低是跟高血脂密切相關的[44-47]。例如，血清總膽固醇(TC)和低密度脂蛋白膽固醇(LDL-C)血中濃度與骨質密度呈負相關。Adami等還發現，全身和髖部的骨質密度與婦女中血清三酸甘油酯呈正相關[45]。

但相反的是，從大型的觀測研究NHAEMS III調查[48]，和來自Framingham研究分析表示血脂直接影響骨質密度的變化微不足道[49]。

由實驗並觀察，低密度脂蛋白膽固醇和高密度脂蛋白膽固醇可能作用於成骨細胞、破骨細胞和血管平滑肌細胞[50,51]。脂質的氧化已被證明在抑制成骨細胞分化[52]，在體外和體內研究皆然[53]。由於未成熟的成骨細胞位於緊鄰的骨血管的內皮下基質，內皮下基質中的脂質蓄積，可預期抑制這些骨形成細胞的分化。此外，氧化的脂質可預期促進骨吸收，隨著氧化的脂質新添和破骨細胞前驅細胞的分化，內皮細胞中單核細胞趨化因子與macrophage colony-stimulating factor (M-CSF)的表現會被誘導。而M-CSF是一種強效的破骨細胞的分化誘導劑。

髖部的去礦化速率和動脈粥樣硬化的速率也已經確定是顯著相關的[54]。動脈粥樣硬化及下肢動脈疾病，可能會導致骨質流失[55]。總和來說，這些研究觀察出脂質有間接作為心血管病和骨質疏鬆症間之連結因素，因促進動脈粥樣硬化形成和動脈狹窄而導致骨質流失，尤其是在與末端動脈血液供應的骨骼部位。

(三)骨質疏鬆症和血管鈣化

19 世紀中，學者第一次描述了心血管疾病和血管鈣化之間的關聯[56]。血管鈣化可能導致破壞性的器官功能障礙，其常見在老化、末期腎衰竭、糖尿病和動脈粥樣硬化。心血管結構的鈣化與動脈硬化、高血壓、心肌缺血、心臟瓣膜疾病和心衰竭有關連。冠狀動脈鈣化與動脈粥樣硬化斑塊形成數量[57,58]，也增加心肌梗塞的風險[59]，和斑塊不穩定呈正相關[60]。血管鈣化與骨質流失共存，有大量的流行病學研究發現且證實這兩種疾病之間的關係[61,62]。

在老年人口中，低骨質密度是增加死亡率的一個危險因子，特別是心血管疾病而來[61]。Framingham心臟研究結果表示，婦女骨質流失者常伴有嚴重的腹主動脈鈣化[63]。主動脈鈣化是一個強的低骨質密度和脆化性骨折的預測因子[62]。

在過去，血管鈣化被認為老化退行性的後果。現在，鈣沉積在血管系統被認為是與骨形成有關的活化和調節的過程[64,65]。然而，骨質疏鬆和血管鈣化之間的關聯是否為因果關係尚未有明確證明。骨與血管組織在分子和細胞的層面上擁有共同幾個特徵。骨保護素(OPG)為抑制破骨細胞的形成，一直被認為是骨骼和血管疾病之間的可能連結[66]。在動脈粥樣硬化的動脈血管壁細胞具分化發展成骨細胞的能力，可演化出各種各樣的骨基質蛋白，包括骨橋蛋白(osteoponti)[67]、骨鈣素(osteocalcin)[68]、基質小泡(matrix vesicles)[69]、和骨形態發生蛋白(bone morphogenetic proteins; BMPs)[70]。Price等推測，骨骼代謝轉換(bone turnover)導致釋放的血中核狀複合物(circulating nucleational complexes)可以解釋在停經後婦女，血管鈣化和骨質疏鬆症之間的關係[71,72]。此外，改變鈣磷的平衡，經鈣調解(calciotropic)激素通過多種機制促進骨流失和血管鈣化[73]，如同副甲狀腺素和維生素D扮演舉足輕重的角色。最後，血管鈣化或動脈粥樣硬化性疾病可能會降低外圍血液供應，導致骨質流失、影響骨代謝、抑制骨細胞的功能、或限制身體活動度。

(四)免疫和發炎的因素

已有些研究探討動脈粥樣硬化的標誌物和骨疾病之間的關係。骨質流失與心血管疾病的關聯性，刺激了研究搜索連接骨骼和血管系統的共同(common)介質。動脈粥樣硬化鈣化是一個受調控的過程，有許多類似骨形成和骨吸收的細胞機制參與。流行病學和臨床研究的資料顯示，動脈粥樣硬化本質上是一個多重危險因素造成的發炎反應，這種反應的後果可能導致心血管疾患。動脈粥樣硬化形成因素包括發炎細胞激素(inflammatory cytokine)，如介白素1(IL-1)、介白素6 (IL-6)、腫瘤壞死因子(TNF)、發炎反應蛋白(CRP)等[74-76]。骨骼代謝轉換的過程中，發炎反應對骨生理和骨重塑(bone remodeling)有重大的影響，因而誘發骨質疏鬆[77,78]。發炎反應標誌物除與動脈粥樣硬化有關係，扮演在血管鈣化的重要角色，也被證明可預測對骨質密度變化[79]。成骨細胞在血管壁中之存在已有證明[80]。骨細胞所產生的調節蛋白質中，包括骨鈣素(osteocalcin)，骨橋蛋白(osteopontin)，

骨保護素(OPG)，核因數K-B受體活化因數配體(RANKL)和骨形態發生蛋白(BMPs)在動脈粥樣硬化病變處均可發現[81]，這表示這些蛋白質不僅在調節骨細胞，也作用在動脈粥樣硬化鈣化形成[82]。

骨保護素(OPG)是腫瘤壞死因子受體家族的蛋白質，通過抑制RANKL調節破骨細胞形成，而這是一個骨重塑關鍵因素[83]。它可以防止RANKL和破骨細胞上的受體結合，從而抑制破骨細胞形成。而骨保護素主要發現在骨骼，心臟和動脈等部位[84]。OPG不僅是破骨細胞形成抑制劑，也是一種發炎細胞激素並牽涉動脈鈣化、動脈粥樣硬化和心血管疾病[85]。例如，骨保護素引發冠狀動脈鈣化斑塊，而與冠狀動脈造影疾病的嚴重程度，和心血管事件的獨立傳統危險因子相關聯[86,87]。這些研究結果表示，加速的骨質流失和增加血管鈣化可能會使OPG代償性反應增加，因而OPG可以作為骨質疏鬆症和心血管疾病的一個標記。

(五)心衰竭和骨質疏鬆症

心衰竭和骨質疏鬆症是中老年人常見的慢性疾病，二者都有很不利的發病率和死亡率，也造成影響生活品質的下降。許多末期心血管疾病患者有骨質疏鬆症的危險因素，如年齡較大和缺乏身體活動。

在心衰竭患者中，心射出率(ejection fraction)和心衰竭(NYHA class)的嚴重程度有顯著關聯性[19]。心衰竭患者的骨質密度降低可能是由於多種因素造成的。身體活動度是骨骼健康的重要決定因素。在心衰竭患者，特別是那些有更多的共病症，如身體活動較少、更高的失能，和非心衰竭老年個體相比虛弱指數較高(frailty scores)者[19]，身體活動能力和虛弱指數都與較低骨質密度、低維生素D和高的促發炎細胞激素具有關聯性[88]。而發炎細胞激素、腫瘤壞死因子、CRP和IL-6在心衰竭血中濃度顯著增加，心衰竭患者也具有較高的虛弱指數[89,90]。在心衰竭患者中，維生素D較低可能是歸因於缺乏陽光下暴曬，較少的身體活動度，減少肝臟合成，腎功能的變化或腸道吸收受損[19]。維生素D不足通常會導致在增加的副甲狀腺素(PTH)分泌，以保持鈣穩定。心衰竭NYHA分級嚴重度和副甲狀腺素亢進之間的關係也已經有報告[91,92]。

二、心臟用藥影響骨骼方面

我們對心血管疾病的發展機制的理解已有重要進展，而幾個同樣的機制也存在於骨質疏鬆症。藥物用來治療心血管疾病，可能產生有益或有害於骨骼健康的結果。

(一) ACEIs/ARBs

RAS支配身上的體液、電解質平衡和血壓[93]。腎素經由腎臟的腎小球旁器(juxtaglomerular apparatus)分泌到血液循環中，裂解血管收縮素原轉成血管收縮素I，然後經由ACE裂解以生成血管收縮素Ⅱ。ACEIs作用於生成的血管收縮素Ⅱ的關鍵酶，而ARB類藥物直接作用於血管收縮素Ⅱ受體。抑制RAS已經被證明是有益於患者的動脈粥樣硬化、高血壓、急性心肌梗塞、慢性收縮性心臟衰竭、中風和糖尿病腎病變等[94-98]。

如前文所述，所述RAS在骨代謝和高血壓相關的骨質疏鬆症有扮演重要的角色。因此，可以合理地推測RAS的阻斷可以改善骨質疏鬆症和高血壓。以前的動物和流行病學研究報導也曾描述ACEIs的益處，包括增加骨量和降低骨折的風險[31,32,34,35]。在3887個中國老年患者的橫斷面研究中，在校正了年齡、體重、身高、thiazide類、β受體阻斷劑、鈣通道阻斷劑、statin類藥物、糖皮質激素、鈣補充劑使用、糖尿病史、心臟疾病、周圍血管疾病、吸煙、飲酒和體力活動能力後，使用ACEIs的與較高的BMD有相關性[31]。但是，ARB類藥物治療對骨量的影響，在動物研究結果並不一致[33,34,99]。ARB於調節骨細胞能力和降低人體中骨折發生率尚未明確。Aoki等指出，ARB類藥物在高血壓和失能臥床女性老人治療後，可顯著減緩股骨頸骨質疏鬆[100]。

(二) β-blockers

據實驗證明，骨重塑可能部分是由交感神經系統控制的[101-103]。在骨頭的交感神經纖維，已被發現和位於成骨細胞和破骨細胞上的腎上腺素受體相關[102]。一個動物研究出，瘦素相關

(leptin-dependent)的神經調控透過交感神經刺激骨形成，有治療骨質疏鬆症潛在的意義[103]。由瘦素刺激的交感神經系統，可通過位於成骨母細胞β腎上腺接受體來調節骨吸收，從而增加了RANKL的分泌和產生，來促進破骨細胞的分化[104]。儘管交感神經系統在調節骨量的機制已相對明確，用β受體阻斷劑來調節人類的骨細胞功能和降低骨折發生率還沒有被認定。

並非所有的研究都發現，β受體阻斷劑的使用和骨折之間存在顯著關聯。一些觀測資料庫和病例對照研究，用β受體阻斷劑可降低骨折的風險[35,105,106]。而其他觀測性研究並沒有發現顯著的關聯性[107-109]。來自澳大利亞Dubbo骨質疏鬆症流行病學研究(N =3488)中獲得的數據顯示與β受體阻斷劑的使用，獨立於身體質量指數(BMI)、骨質密度、年齡以及其他影響因素相關骨折的風險之外顯著降低骨折風險[105]。大型的病例對照分析(N=30601)也發現，在體重指數、吸煙狀況、以及使用其他類降壓藥物調整後，β-受體阻斷劑的使用讓骨折的風險大大降低[106]。一項整合性分析研究包括β受體阻斷劑的7項研究，結果顯示的結論是β受體阻斷劑的使用與骨折風險顯著下降有關[110]。一項研究指出，β1 selective β-受體阻斷劑較其他抗血壓藥類在老年人口上有骨折風險顯著下降[111]。但是，另一個整合性分析研究在β受體阻斷劑為心臟衰竭的臨床試驗中，對骨折下降發生率產生懷疑[112]。因此，尚無足夠的證據顯示β受體阻斷劑可作為骨質疏鬆症的治療，也不能作為骨折風險的危險因素。β受體阻斷劑現仍有迷思，未來需要以骨折作為實驗終點(end point)，且明確、隨機的、雙盲對照性臨床試驗來解決。

(三) Statins

Statins藥物被廣泛地用於高膽固醇血症的治療。它們抑制3-hydroxy-3-methylglutarylcoenzyme A 還原酶，並降低肝的膽固醇合成[113]。Statins藥物同時具有抗動脈硬化作用和有益的多效性(pleiotropic effects)。因此，statins藥物降低心血管疾病的發病率效果顯著[114]。此外，statin類藥物可能對骨代謝有影響。Statin類藥物在骨代謝中的作用是在1999年首先提出的，當時有人用口服statin類藥物治療老鼠，因而增加鬆質骨(cancellous bone)量[115]。現已經認定，膽固醇的合成和破骨細胞的活化都涉及相同的生化訊息途徑[115,116]。Statin類藥物是經由防止mevalonate酸的產生來防止破骨細胞的活化[115]。反過來，骨重塑減少，骨吸收降低，骨吸收和骨形成的平衡被恢復。一個動物研究指出，Statin類藥物可能會增加骨形成[22]。因此，患者骨質疏鬆症的風險可能會受益於statin類藥物治療。

一些觀測研究和病例對照研究表明，Statin類藥物的服用與骨折的風險降低有關[117-119]。Chan等人發現，Statin類藥物似乎可預防老年婦女在非病理性骨折[117]。Meier等人發現服用statin類藥物，於大於50歲的人有降低骨折的風險[118]。同樣，老年患者髖部骨折的風險降低，也有報導與statin類藥物的使用之間有關聯性[119]。然而，並非所有的研究重現這種關聯性[120,121]。在英國，一個大型病例對照分析(N=163760)研究發現，statin類藥物處方的劑量在臨床運用上並沒有相關降低骨折的風險[120]。一項研究提出，對患有缺血性心臟疾病隨機分配pravastatin或安慰劑的研究提供了statin類藥物對骨折的風險，其結果顯著不支持降低風險[121]。然而應當指出的是，這項研究並不涉及骨質疏鬆的人群。

總之，statin類藥物影響骨生物學上的機制已經被合理的認同，也在體外研究上證明增加成骨母細胞分化和骨形成。未來需要前瞻性隨機對照試驗，以更好地描述statin類藥物在骨質疏鬆症的作用。

(四) Thiazide Diuretics

Thiazide仍然是利尿劑中最廣泛使用於治療高血壓的藥[20]。這些藥劑用於抑制鈉和氯的再吸收，促進鈣的重吸收，產生一個正鈣平衡，這被預計可能對骨質密度有正面效果。

並不是所有的觀察性研究都發現，使用thiazide利尿劑和骨折之間的有顯著的關聯性[122,123]。不一致的結果，可能反映了保護作用可能只表現長時間使用後或者沒堅持治療而停止使用thiazide利尿劑[108,124-126]。一項前瞻性研究中老年男性和女性，認為使用thiazide利

尿藥與減少大約三分之一髖部骨折的風險[125]。Schoof等人建議，thiazide利尿劑防止髖部骨折，但停止使用後4個月內這種保護作用則消失[126]。已經有thiazide利尿劑和BMD的兩個前瞻性隨機試驗。Bolland等人表示，在健康的停經後婦女thiazide治療有益骨質密度[127]。LaCroix等人表示，也發現用低劑量的hydrochlorothiazide，可維持健康老年人的骨質密度[128]。

(五) Loop Diuretics

Loop利尿劑主要用於心衰竭體液超量的治療。Loop利尿劑作用是抑制Henle環上升枝氯和鈉的再吸收中，並且還抑制鎂和鈣的重吸收。減少鈣在腎臟重吸收，雖然可能通過增加PTH活性來促成1,25 dihdroxyvitamin D的合成增加，和胃腸道對鈣的吸收，但這一連串的變化最有可能導致對骨健康具有負面影響[129]。

一項老年男性和女性的前瞻性研究，中老年婦女已被確定在loop利尿劑的使用有較低骨質密度[130]，也增加了髖部的骨質流失的危險因素[129,131]。一些觀察性研究也描述了使用loop利尿劑之後和增加骨折之間的關聯性[123, 132]。這些結果建議了，在臨床上loop利尿劑在老年患者中，對有骨流失的可能性時應予以考慮使用。

結　論

總之，骨質疏鬆症與高血壓、血脂代謝異常、以及心血管疾病的風險相關，這種現象可由發炎反應、動脈粥樣硬化、血管鈣化來驅使，並因此而增加動脈硬化之關聯性。近年來在解釋骨質疏鬆症、骨折、與心血管疾病共同的危險因素和病理生理關係已經有了重大進展。

不同的研究已經呈現出廣泛用於心血管疾病藥物的影響，如statin類藥物和抗高血壓藥物，包括ACEIs/ARBs類藥物、β-blockers和thiazide利尿劑對骨代謝的影響。更進一步理解病理生理機制，將有助於同時對骨代謝和心血管疾病發展未來的治療方法。

參考文獻

1. Seeman E, Delmas PD. Bone quality--the material and structural basis of bone strength and fragility. N Engl J Med 2006; 354: 2250-61.
2. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ 2006; 174: 801-9.
3. Farhat GN, Newman AB, Sutton-Tyrrell K, et al. The association of bone mineral density measures with incident cardiovascular disease in older adults. Osteoporos Int 2007; 18: 999-1008.
4. Kado DM, Browner WS, Blackwell T, Gore R, Cummings SR. Rate of bone loss is associated with mortality in older women: a prospective study. J Bone Miner Res 2000; 15: 1974-80.
5. Gupta G, Aronow WS. Atherosclerotic vascular disease may be associated with osteoporosis or osteopenia in postmenopausal women: a preliminary study. Arch Gerontol Geriatr 2006; 43: 285-8.
6. Ness J, Aronow WS. Comparison of prevalence of atherosclerotic vascular disease in postmenopausal women with osteoporosis or osteopenia versus without osteoporosis or osteopenia. Am J Cardiol 2006; 97: 1427-8.
7. Sennerby U, Melhus H, Gedeborg R, et al. Cardiovascular diseases and risk of hip fracture. JAMA 2009; 302: 1666-73.
8. Magnus JH, Broussard DL. Relationship between bone mineral density and myocardial infarction in US adults. Osteoporos Int 2005; 16: 2053-62.
9. Barengolts EI, Berman M, Kukreja SC, Kouznetsova T, Lin C, Chomka EV. Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. Calcif Tissue Int 1998; 62: 209-13.
10. Broussard DL, Magnus JH. Coronary heart disease risk and bone mineral density among U.S. women and men. J Womens Health (Larchmt) 2008; 17: 479-90.
11. Varma R, Aronow WS, Basis Y, et al. Relation of bone mineral density to frequency of coronary heart disease. Am J Cardiol 2008; 101: 1103-4.
12. Marcovitz PA, Tran HH, Franklin BA, et al. Usefulness of bone mineral density to predict significant coronary artery disease. Am J Cardiol 2005; 96: 1059-63.
13. Erbilen E, Yazici S, Ozhan H, Bulur S, Ordu S, Yazici M. Relationship between angiographically documented coronary artery disease and low bone mass in men. Circ J 2007; 71: 1095-8.
14. Woo J, Kwok T, Leung J, Tang N. Dietary intake, blood pressure and osteoporosis. J Hum Hypertens 2009; 23: 451-5.
15. Resnick LM, Laragh JH, Sealey JE, Alderman MH. Divalent cations in essential hypertension. Relations between serum ionized calcium, magnesium, and plasma renin activity. N Engl J Med 1983; 309: 888-91.
16. Cappuccio FP, Kalaitzidis R, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. J

Nephrol 2000; 13: 169-77.
17. Tanko LB, Bagger YZ, Christiansen C. Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. Calcif Tissue Int 2003; 73: 15-20.
18. Choi SH, An JH, Lim S, et al. Lower bone mineral density is associated with higher coronary calcification and coronary plaque burdens by multidetector row coronary computed tomography in pre- and postmenopausal women. Clin Endocrinol (Oxf) 2009; 71: 644-51.
19. Abou-Raya S, Abou-Raya A. Osteoporosis and congestive heart failure (CHF) in the elderly patient: double disease burden. Arch Gerontol Geriatr 2009; 49: 250-4.
20. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72.
21. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349: 1269-76.
22. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990; 335: 827-38.
23. Lifton RP. Molecular genetics of human blood pressure variation. Science 1996; 272: 676-80.
24. Ralston SH, de Crombrugghe B. Genetic regulation of bone mass and susceptibility to osteoporosis. Genes Dev 2006; 20: 2492-506.
25. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA. High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of Osteoporotic Fractures Research Group. Lancet 1999; 354: 971-5.
26. Mussolino ME, Gillum RF. Bone mineral density and hypertension prevalence in postmenopausal women: results from the Third National Health and Nutrition Examination Survey. Ann Epidemiol 2006; 16: 395-9.
27. Lee HT, Shin J, Min SY, et al. The relationship between bone mineral density and blood pressure in the Korean elderly population: the Korea National Health and Nutrition Examination Survey, 2008-2011. Clin Exp Hypertens 2014: 1-6.
28. Strazzullo P, Nunziata V, Cirillo M, et al. Abnormalities of calcium metabolism in essential hypertension. Clin Sci (Lond) 1983; 65: 137-41.
29. Perez-Castrillon JL, Justo I, Silva J, et al. Bone mass and bone modelling markers in hypertensive postmenopausal women. J Hum Hypertens 2003; 17: 107-10.
30. McCarron DA, Pingree PA, Rubin RJ, Gaucher SM, Molitch M, Krutzik S. Enhanced parathyroid function in essential hypertension: a homeostatic response to a urinary calcium leak. Hypertension 1980; 2: 162-8.
31. Lynn H, Kwok T, Wong SY, Woo J, Leung PC. Angiotensin converting enzyme inhibitor use is associated with higher bone mineral density in elderly Chinese. Bone 2006; 38: 584-8.
32. Shimizu H, Nakagami H, Osako MK, et al. Prevention of osteoporosis by angiotensin-converting enzyme inhibitor in spontaneous hypertensive rats. Hypertens Res 2009; 32: 786-90.
33. Izu Y, Mizoguchi F, Kawamata A, et al. Angiotensin II type 2 receptor blockade increases bone mass. J Biol Chem 2009; 284: 4857-64.
34. Asaba Y, Ito M, Fumoto T, et al. Activation of renin-angiotensin system induces osteoporosis independently of hypertension. J Bone Miner Res 2009; 24: 241-50.
35. Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. J Hypertens 2006; 24: 581-9.
36. Hatton R, Stimpel M, Chambers TJ. Angiotensin II is generated from angiotensin I by bone cells and stimulates osteoclastic bone resorption in vitro. J Endocrinol 1997; 152: 5-10.
37. Hiruma Y, Inoue A, Hirose S, Hagiwara H. Angiotensin II stimulates the proliferation of osteoblast-rich populations of cells from rat calvariae. Biochem Biophys Res Commun 1997; 230: 176-8.
38. Shimizu H, Nakagami H, Osako MK, et al. Angiotensin II accelerates osteoporosis by activating osteoclasts. FASEB J 2008; 22: 2465-75.
39. Teitelbaum SL. Bone resorption by osteoclasts. Science 2000; 289: 1504-8.
40. Tintut Y, Parhami F, Tsingotjidou A, Tetradis S, Territo M, Demer LL. 8-Isoprostaglandin E2 enhances receptor-activated NFkappa B ligand (RANKL)-dependent osteoclastic potential of marrow hematopoietic precursors via the cAMP pathway. J Biol Chem 2002; 277: 14221-6.
41. Tintut Y, Parhami F, Le V, Karsenty G, Demer LL. Inhibition of osteoblast-specific transcription factor Cbfa1 by the cAMP pathway in osteoblastic cells. Ubiquitin/proteasome-dependent regulation. J Biol Chem 1999; 274: 28875-9.
42. Guan XX, Zhou Y, Li JY. Reciprocal roles of angiotensin II and Angiotensin II Receptors Blockade (ARB) in regulating Cbfa1/RANKL via cAMP signaling pathway: possible mechanism for hypertension-related osteoporosis and antagonistic effect of ARB on hypertension-related osteoporosis. Int J Mol Sci 2011; 12: 4206-13.
43. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive summary of she third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001; 285: 2486-97.
44. Broulik PD, Kapitola J. Interrelations between body weight, cigarette smoking and spine mineral density in osteoporotic Czech women. Endocr Regul 1993; 27: 57-60.
45. Adami S, Braga V, Zamboni M, et al. Relationship between lipids and bone mass in 2 cohorts of healthy women and men. Calcif Tissue Int 2004; 74: 136-42.
46. Brownbill RA, Ilich JZ. Lipid profile and bone paradox: higher serum lipids are associated with higher bone mineral density in postmenopausal women. J Womens Health (Larchmt) 2006; 15: 261-70.

47. Cui LH, Shin MH, Chung EK, et al. Association between bone mineral densities and serum lipid profiles of pre- and post-menopausal rural women in South Korea. Osteoporos Int 2005; 16: 1975-81.
48. Solomon DH, Avorn J, Canning CF, Wang PS. Lipid levels and bone mineral density. Am J Med 2005; 118: 1414.
49. Samelson EJ, Cupples LA, Hannan MT, et al. Long-term effects of serum cholesterol on bone mineral density in women and men: the Framingham Osteoporosis Study. Bone 2004; 34: 557-61.
50. Parhami F, Basseri B, Hwang J, Tintut Y, Demer LL. High-density lipoprotein regulates calcification of vascular cells. Circ Res 2002; 91: 570-6.
51. Tintut Y, Morony S, Demer LL. Hyperlipidemia promotes osteoclastic potential of bone marrow cells ex vivo. Arterioscler Thromb Vasc Biol 2004; 24: e6-10.
52. Parhami F, Jackson SM, Tintut Y, et al. Atherogenic diet and minimally oxidized low density lipoprotein inhibit osteogenic and promote adipogenic differentiation of marrow stromal cells. J Bone Miner Res 1999; 14: 2067-78.
53. Parhami F, Tintut Y, Beamer WG, Gharavi N, Goodman W, Demer LL. Atherogenic high-fat diet reduces bone mineralization in mice. J Bone Miner Res 2001; 16: 182-8.
54. Bagger YZ, Tanko LB, Alexandersen P, Qin G, Christiansen C, Prospective Epidemiological Risk Factors Study G. Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J Intern Med 2006; 259: 598-605.
55. Laroche M, Pouilles JM, Ribot C, et al. Comparison of the bone mineral content of the lower limbs in men with ischaemic atherosclerotic disease. Clin Rheumatol 1994; 13: 611-4.
56. Virchow R. Cellular pathology. As based upon physiological and pathological histology. Lecture XVI--Atheromatous affection of arteries. 1858. Nutr Rev 1989; 47: 23-5.
57. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995; 92: 2157-62.
58. Sangiorgi G, Rumberger JA, Severson A, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 1998; 31: 126-33.
59. Loecker TH, Schwartz RS, Cotta CW, Hickman JR, Jr. Fluoroscopic coronary artery calcification and associated coronary disease in asymptomatic young men. J Am Coll Cardiol 1992; 19: 1167-72.
60. Fitzgerald PJ, Ports TA, Yock PG. Contribution of localized calcium deposits to dissection after angioplasty. An observational study using intravascular ultrasound. Circulation 1992; 86: 64-70.
61. von der Recke P, Hansen MA, Hassager C. The association between low bone mass at the menopause and cardiovascular mortality. Am J Med 1999; 106: 273-8.
62. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 2004; 89: 4246-53.
63. Kiel DP, Kauppila LI, Cupples LA, Hannan MT, O'Donnell CJ, Wilson PW. Bone loss and the progression of abdominal aortic calcification over a 25 year period: the Framingham Heart Study. Calcif Tissue Int 2001; 68: 271-6.
64. Doherty TM, Asotra K, Fitzpatrick LA, et al. Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. Proc Natl Acad Sci U S A 2003; 100: 11201-6.
65. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. Arterioscler Thromb Vasc Biol 2004; 24: 1161-70.
66. Bucay N, Sarosi I, Dunstan CR, et al. osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 1998; 12: 1260-8.
67. Giachelli CM, Bae N, Almeida M, Denhardt DT, Alpers CE, Schwartz SM. Osteopontin is elevated during neointima formation in rat arteries and is a novel component of human atherosclerotic plaques. J Clin Invest 1993; 92: 1686-96.
68. Levy RJ, Schoen FJ, Levy JT, Nelson AC, Howard SL, Oshry LJ. Biologic determinants of dystrophic calcification and osteocalcin deposition in glutaraldehyde-preserved porcine aortic valve leaflets implanted subcutaneously in rats. Am J Pathol 1983; 113: 143-55.
69. Tanimura A, McGregor DH, Anderson HC. Matrix vesicles in atherosclerotic calcification. Proc Soc Exp Biol Med 1983; 172: 173-7.
70. Bostrom K, Watson KE, Horn S, Wortham C, Herman IM, Demer LL. Bone morphogenetic protein expression in human atherosclerotic lesions. J Clin Invest 1993; 91: 1800-9.
71. Price PA, Caputo JM, Williamson MK. Bone origin of the serum complex of calcium, phosphate, fetuin, and matrix Gla protein: biochemical evidence for the cancellous bone-remodeling compartment. J Bone Miner Res 2002; 17: 1171-9.
72. Price PA, Faus SA, Williamson MK. Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. Arterioscler Thromb Vasc Biol 2001; 21: 817-24.
73. Giachelli CM. Vascular calcification mechanisms. J Am Soc Nephrol 2004; 15: 2959-64.
74. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. Circulation 2003; 107: 398-404.
75. Adamopoulos IE, Mellins ED. Alternative pathways of osteoclastogenesis in inflammatory arthritis. Nat Rev Rheumatol 2015; 11: 189-94.
76. D'Amico L, Roato I. Cross-talk between T cells and osteoclasts in bone resorption. Bonekey Rep 2012; 1: 82.
77. Arron JR, Choi Y. Bone versus immune system. Nature 2000; 408: 535-6.
78. Lorenzo J. Interactions between immune and bone cells:

new insights with many remaining questions. J Clin Invest 2000; 106: 749-52.
79. Ding C, Parameswaran V, Udayan R, Burgess J, Jones G. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: a longitudinal study. J Clin Endocrinol Metab 2008; 93: 1952-8.
80. Watson KE, Bostrom K, Ravindranath R, Lam T, Norton B, Demer LL. TGF-beta 1 and 25-hydroxycholesterol stimulate osteoblast-like vascular cells to calcify. J Clin Invest 1994; 93: 2106-13.
81. Dhore CR, Cleutjens JP, Lutgens E, et al. Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 2001; 21: 1998-2003.
82. Xiao XH, Liao EY, Zhou HD, Dai RC, Yuan LQ, Wu XP. Ascorbic acid inhibits osteoclastogenesis of RAW264.7 cells induced by receptor activated nuclear factor kappaB ligand (RANKL) in vitro. J Endocrinol Invest 2005; 28: 253-60.
83. Schoppet M, Preissner KT, Hofbauer LC. RANK ligand and osteoprotegerin: paracrine regulators of bone metabolism and vascular function. Arterioscler Thromb Vasc Biol 2002; 22: 549-53.
84. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997; 89: 309-19.
85. McFarlane SI, Muniyappa R, Shin JJ, Bahtiyar G, Sowers JR. Osteoporosis and cardiovascular disease: brittle bones and boned arteries, is there a link? Endocrine 2004; 23: 1-10.
86. Kiechl S, Schett G, Wenning G, et al. Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. Circulation 2004; 109: 2175-80.
87. Jono S, Ikari Y, Shioi A, et al. Serum osteoprotegerin levels are associated with the presence and severity of coronary artery disease. Circulation 2002; 106: 1192-4.
88. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002; 162: 2333-41.
89. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). Am J Cardiol 2003; 92: 522-8.
90. Reuben DB, Cheh AI, Harris TB, et al. Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. J Am Geriatr Soc 2002; 50: 638-44.
91. Garakyaraghi M, Kerdegari M, Siavash M. Calcium and vitamin D status in heart failure patients in Isfahan, Iran. Biol Trace Elem Res 2010; 135: 67-73.
92. Bozic B, Loncar G, Prodanovic N, et al. Parathyroid hormone response to vitamin D insufficiency in elderly males with chronic heart failure. Physiol Res 2011; 60 Suppl 1: S155-63.
93. Peach MJ. Renin-angiotensin system: biochemistry and mechanisms of action. Physiol Rev 1977; 57: 313-70.
94. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004; 363: 2022-31.
95. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 995-1003.
96. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145-53.
97. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008; 359: 2417-28.
98. Bulpitt CJ, Beckett NS, Cooke J, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. J Hypertens 2003; 21: 2409-17.
99. Gealh WC, Pereira CC, Luvizuto ER, Garcia-Junior IR, Antoniali C, Okamoto R. Healing process of autogenous bone graft in spontaneously hypertensive rats treated with losartan: an immunohistochemical and histomorphometric study. J Oral Maxillofac Surg 2014; 72: 2569-81.
100. Aoki M, Kawahata H, Sotobayashi D, et al. Effect of angiotensin II receptor blocker, olmesartan, on turnover of bone metabolism in bedridden elderly hypertensive women with disuse syndrome. Geriatr Gerontol Int 2014.
101. Yadav VK, Oury F, Suda N, et al. A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. Cell 2009; 138: 976-89.
102. Togari A. Adrenergic regulation of bone metabolism: possible involvement of sympathetic innervation of osteoblastic and osteoclastic cells. Microsc Res Tech 2002; 58: 77-84.
103. Takeda S, Elefteriou F, Levasseur R, et al. Leptin regulates bone formation via the sympathetic nervous system. Cell 2002; 111: 305-17.
104. Elefteriou F, Ahn JD, Takeda S, et al. Leptin regulation of bone resorption by the sympathetic nervous system and CART. Nature 2005; 434: 514-20.
105. Yang S, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Association between beta-blocker use and fracture risk: the Dubbo Osteoporosis Epidemiology Study. Bone 2011; 48: 451-5.
106. Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. Use of beta-blockers and risk of fractures. JAMA 2004; 292: 1326-32.
107. Levasseur R, Dargent-Molina P, Sabatier JP, Marcelli C, Breart G. Beta-blocker use, bone mineral density, and fracture risk in older women: results from the Epidemiologie de l'Osteoporose prospective study. J Am Geriatr Soc 2005; 53: 550-2.
108. Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. J Bone Miner Res 2011; 26: 1561-7.

109. Reid IR, Gamble GD, Grey AB, et al. Beta-Blocker use, BMD, and fractures in the study of osteoporotic fractures. J Bone Miner Res 2005; 20: 613-8.
110. Wiens M, Etminan M, Gill SS, Takkouche B. Effects of antihypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. J Intern Med 2006; 260: 350-62.
111. Song HJ, Lee J, Kim YJ, et al. beta1 selectivity of beta-blockers and reduced risk of fractures in elderly hypertension patients. Bone 2012; 51: 1008-15.
112. Reid IR. Effects of beta-blockers on fracture risk. J Musculoskelet Neuronal Interact 2008; 8: 105-10.
113. Endo A. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res 1992; 33: 1569-82.
114. Vaughan CJ, Gotto AM, Jr., Basson CT. The evolving role of statins in the management of atherosclerosis. J Am Coll Cardiol 2000; 35: 1-10.
115. Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. Science 1999; 286: 1946-9.
116. Fisher JE, Rogers MJ, Halasy JM, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. Proc Natl Acad Sci U S A 1999; 96: 133-8.
117. Chan KA, Andrade SE, Boles M, et al. Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. Lancet 2000; 355: 2185-8.
118. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. JAMA 2000; 283: 3205-10.
119. Wang PS, Solomon DH, Mogun H, Avorn J. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. JAMA 2000; 283: 3211-6.
120. van Staa TP, Wegman S, de Vries F, Leufkens B, Cooper C. Use of statins and risk of fractures. JAMA 2001; 285: 1850-5.
121. Reid IR, Hague W, Emberson J, et al. Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. Long-term Intervention with Pravastatin in Ischaemic Disease. Lancet 2001; 357: 509-12.
122. Cauley JA, Cummings SR, Seeley DG, et al. Effects of thiazide diuretic therapy on bone mass, fractures, and falls. The Study of Osteoporotic Fractures Research Group. Ann Intern Med 1993; 118: 666-73.
123. Heidrich FE, Stergachis A, Gross KM. Diuretic drug use and the risk for hip fracture. Ann Intern Med 1991; 115: 1-6.
124. Ray WA, Griffin MR, Downey W, Melton LJ, 3rd. Long-term use of thiazide diuretics and risk of hip fracture. Lancet 1989; 1: 687-90.
125. LaCroix AZ, Wienpahl J, White LR, et al. Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med 1990; 322: 286-90.
126. Schoofs MW, van der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. Ann Intern Med 2003; 139: 476-82.
127. Bolland MJ, Ames RW, Horne AM, Orr-Walker BJ, Gamble GD, Reid IR. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. Osteoporos Int 2007; 18: 479-86.
128. LaCroix AZ, Ott SM, Ichikawa L, Scholes D, Barlow WE. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000; 133: 516-26.
129. Rejnmark L, Vestergaard P, Heickendorff L, Andreasen F, Mosekilde L. Effects of long-term treatment with loop diuretics on bone mineral density, calcitropic hormones and bone turnover. J Intern Med 2005; 257: 176-84.
130. Ooms ME, Lips P, Van Lingen A, Valkenburg HA. Determinants of bone mineral density and risk factors for osteoporosis in healthy elderly women. J Bone Miner Res 1993; 8: 669-75.
131. Lim LS, Fink HA, Kuskowski MA, et al. Loop diuretic use and increased rates of hip bone loss in older men: the Osteoporotic Fractures in Men Study. Arch Intern Med 2008; 168: 735-40.
132. Tromp AM, Ooms ME, Popp-Snijders C, Roos JC, Lips P. Predictors of fractures in elderly women. Osteoporos Int 2000; 11: 134-40.

Bone Loss And Cardiovascular Disease

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Osteoporosis and cardiovascular disease (CVD) were thought to be separate chronic diseases, traditionally. More and more new evidence current supports a direct association between osteoporosis and hypertension, atherosclerosis, dyslipidemia, congestive heart failure, and vascular calcification. Several developments have been made in recent years in clarify the pathophysiological relationship and common risk factors between CVD and osteoporosis. An upgraded understanding of the pathophysiological mechanisms corporate to these conditions may contribute to future development of therapies that can benefit on both bone metabolism and CVD. (J Intern Med Taiwan 2015; 26: 77-87)