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糖尿病与骨质疏松相关性研究进展

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摘　要

糖尿病(DM, diabetes mellitus)和骨质疏松症(OP, osteoporosis)是两种有差异的疾病，有不同的并发症。长期慢性高血糖的刺激引起、脂质沉积、血供差、葡萄糖毒性以及氧化应激的联合作用可导致骨质疏松的发生；除了糖尿病患者可以发生骨质疏松，其他导致或缓解糖尿病的药物也可以引起骨质疏松；例如：皮质醇激素，免疫抑制剂，利尿剂，降钙素等药物有着相似的致病途径。目的：从发病机制和药物相互作用研究糖尿病与骨质疏松相关性。

关键词

糖尿病，相关性，骨质疏松，机制，药物

Research Progress on Correlation between Diabetes Mellitus and Osteoporosis

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Abstract

Diabetes mellitus (DM) and osteoporosis (OP) are two different diseases with different complications. The combined effects of chronic hyperglycemia, lipid deposition, poor blood supply, glucose toxicity and oxidative stress can lead to osteoporosis. In addition to diabetes patients, other drugs that cause or relieve diabetes can also cause osteoporosis; Drugs such as cortisol, immunosuppressants, diuretics, and calcitonin have similar pathways. Objective: To study the relationship between diabetes mellitus and osteoporosis from the perspective of pathogenesis and drug interaction.

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Keywords

Diabetes Mellitus, Correlation, Osteoporosis, Mechanism, Drug

1. 引言

糖尿病：糖尿病可以引起糖代谢、脂肪代谢、蛋白质代谢均出现异常，损害机体很多脏器。骨质疏松症：世界卫生组织将其定义为一种由于骨量低和显微结构恶化，导致骨强度降低和骨折风险增加的疾病。骨折是其最严重的并发症。[1]尽管采取了不同的治疗策略，但对这些疾病的控制和减轻其负担的效果并不令人满意，特别是当它们相继出现时。糖尿病导致骨质疏松患病率是 40%~66%。本文旨在阐明这两种主要疾病的相似之处。基于不同的实验发现，我们想阐明相似途径导致糖尿病和骨质疏松症。

2. 糖尿病引起骨质疏松机制

糖尿病与慢性血糖升高有关。持续的高血糖诱导氧化应激和毒性，破坏少数存活的胰腺 β 细胞，导致 DM [2]的进一步恶化。慢性高血糖会导致严重的蛋白质代谢、脂质、和碳水化合物障碍。脂质代谢的破坏引起极低密度脂蛋白(VLDL)和总胆固醇(TC) [3]的水平升高，进一步引起 VLDL 和 TC 在亚内皮细胞层和内皮细胞层聚集。积累的脂肪会引起动脉粥样硬化和血管管腔狭窄。血管结构和功能受损会影响大量器官的血液流动，包括但不限于骨骼、视网膜、肾脏、中枢和外周神经系统的神经元，以及其他重要组织和器官，如心脏[3]。在血管内皮下层 VLDL 持续、长期沉积，将引起大、微血管病变，引起骨供血不足[3]。如果血管系统较差，骨组织血供受到影响，将不能正常工作，并可能出现结构异常，如微裂纹。氧化应激是糖尿病并发症的可能原因。另一个可能导致糖尿病并发症的因素是高血糖诱导的氧化应激[4]。普遍认为，在慢性高血糖刺激下晚期糖基化终产物(AGE)的形成[3]，进而引起 1 型胶原蛋白和其他负责骨完整性的生物因子形成的分子结构发生改变，导致骨量形成受损[5]。一些研究表明 AGE 产物受体(RAGE)通过抑制 PI3、ERK 和 Wnt 等多种信号通路来阻止成骨细胞的增殖[6]。此外，RAGE 是已被证明能够增加破骨细胞的形成，引起骨形成的缺陷[7]。AGE 产物在与 RAGE 结合后的聚合能力导致骨骼蛋白的交叉连接，导致骨骼硬度和脆性[8]。研究表明，糖尿病引起碱性磷酸酶[9]显著降低，是骨形成有关的关键酶，在 DM [10]发病后减少。脂质沉积、血供差、葡萄糖毒性以及氧化应激的联合作用可导致骨质疏松的发生。

3. 常见的相关药物

一些药物，它们在大多数情况下起着相同的作用，但有时却产生相反的效果。考虑 到糖尿病和骨质疏松症之间的相关性，需要在伴随发病或因果条件下更有效地管理 这两种疾病[11]。

3.1. 糖皮质激素

糖皮质激素最著名的引发糖尿病的药物。研究糖皮质激素在诱导高血糖中的作用表明，在糖尿病(同时伴有自身免疫性疾病)和非糖尿病患者中，被药物诱导引起的高血糖发生率是 35%。皮质类固醇强的松

是导致这种不良反应的最普遍的，用于各种自身免疫性疾病。不仅他们的高剂量，而且他们的日常低剂量摄入的自身免疫性疾病导致高血糖。[12]另一项具有相同目的的研究表明，糖皮质激素治疗，无论是口服还是脉冲治疗，都能增加继发性糖尿病的风险达 22.2%。如果短时间内高剂量的皮质类固醇，会在数周内引起糖尿病。此外，药物西糖尿病在空腹血糖较高的患者发生[13]的风险较高。糖皮质激素减少骨细胞中破骨细胞的数量，但是由于其对成骨细胞凋亡的影响作用大于破骨细胞，故而引起骨质疏松和骨坏死[14]。激素诱导的骨质疏松在分子水平上表明，它们可以减弱 AKT 的磷酸化，放大 FoxOs (氧化还原敏感叉头盒 O 转录因子家族)的激活，最终抑制 Wnt/β-catenin 介导的成骨细胞[15]信号通路。糖皮质激素有免疫抑制作用，被广泛和成功地应用于各种炎症条件。骨损害与长期或大剂量使用糖皮质激素相关，引起 GIO 继发性骨质疏松和增加骨折风险。虽然复杂，但其机制涉及在使用糖皮质激素的初始阶段增加破骨细胞功能，随后因成骨细胞和骨细胞凋亡导致骨形成下降。

3.2. 免疫抑制剂

免疫抑制药物，如他克莫司、环孢素、雷帕霉素等，已显示出其潜在的提高血糖浓度和诱发糖尿病的能力，尤其是他克莫司[16] [17] [18]。一项进一步的动物研究证实，他克莫司剂量依赖性(0.5、1 和 5 mg/kg/d，持续使用 14 天)可引起胰岛素抵抗，并促进空肠胰岛素摄取[19]。另一方面，从他克莫司向环孢素转换后，葡萄糖浓度发生改变[20]。此外，对他克莫司对 β-细胞作用的评估表明，它在一定程度上是通过糖脂毒性发生的，并且有可能被逆转[21]。

这组药物可引起骨骼改变和继发性骨质疏松[22] [23] [24]。一项细胞培养研究显示，他克莫司和雷帕霉素，而不是环孢素，会增加成骨细胞凋亡[25]，而一些动物实验研究发现，环孢素(大鼠 10 mg/kg/day)是导致骨丢失的更强原因[26] [27]。

3.3. 利尿剂

噻嗪类是影响远曲小管的利尿药物，也是另一类致糖尿病药物[27] [28]。有研究表明噻嗪类药物治疗后致糖尿病作用，是由于噻嗪类药物治疗后低钾血症引起的[29] [30]。一致地，氯化钾补充显著促进噻嗪类药物患者的高血糖管理[31] [32]。Brown 等人指定了一项研究，研究对象为三组高血压患者，分别接受氢氯噻嗪(25 mg/d)、阿米洛利(10 mg/d，一种保钾利尿剂)、(阿米洛利 5 mg/d 和氢氯噻嗪 12.5 mg/d)。阿米洛利受体和联合治疗的组合具有更好的糖耐量[33]。与前两组药物不同，噻嗪类药物在骨骼系统中具有保护作用，帮助其保持其微结构[34] [35] [36]或至少不会导致骨丢失[37]。这种有益的作用似乎是通过减少尿钙排泄来介导的[38] [39]。因此，噻嗪类药物可以调节肾脏中的葡萄糖和骨代谢。

3.4. 质子泵抑制剂 PPIs

PPIs 是一类重要的被用于抑制胃酸分泌药，广泛应用于消化系统疾病，例如：卓——艾氏综合症胃食管反流病(GERD)，非溃疡性消化不良(NUD)和消化性溃疡病(PUD)等。多数评价 PPIs 对糖尿病患者血糖控制作用的研究表明，PPIs 可能由于胃泌素和胰岛素水平升高，能够部分降低血糖水平，并纠正 HbA1c 水平[40] [41] [42]。除了能更好地控制血糖外，它们还能剂量依赖性地降低 2 型糖尿病的风险[43]。部分胰腺切除和免疫缺陷小鼠胰腺细胞移植的动物模型表明，胃泌素本身，特别是胃泌素和 GLP1 联合作用，是一种有效的胰腺细胞增殖促进剂[44] [45] [46]。在 nod-严重联合免疫缺陷小鼠(NOD-SCID)植入人胰管细胞后，同时给予 PPI(泮托拉唑 40 mg/kg)和二肽基肽酶-4 抑制剂(DPP-4i) (西格列汀 100 mg/kg)可使胃泌素和 GLP1 水平高于正常水平 2~3 倍。这种激素变化使人移植物中的胰岛素和胰岛素染色细胞数量增加了 9~13 倍，与载体处理组相比[47]。

3.5. 降钙素

血浆降钙素原使用方面，存在发生糖尿病和胰岛素抵抗[48]的显著风险。出乎意料的是，胰淀素和降钙素受体激动剂，无论是单独还是联合二甲双胍，都参与了更好地管理糖尿病大鼠[49]的血糖和胰岛素抵抗。在一个动物模型中显示了鲑鱼降钙素(2 mg/kg，淀粉素和降钙素激动剂)在控制空腹和餐后血糖方面的疗效，[50]的代表。老年 2 型糖尿病合并骨质疏松症妇女皮下注射鲑鱼降钙素(50 IU)可增加骨密度 T 评分，降低骨折风险[51]。现如今，鲑鱼降钙素是一种可使用来治疗骨质疏松症和防止其未来在高危人群[52]中发生的药物。由于降钙素对糖尿病有潜在的影响，它可以被作为另一种控制糖尿病－骨质疏松症的候选药物。

4. 展望与结语

为了在伴随发病或因果条件下更有效地管理这两种疾病，对于临床上易引起糖尿病和骨质疏松的药物，对于糖尿病及骨质疏松治疗用药需全面谨慎地选择，了解了某些药物存在同时导致骨质疏松和糖尿病的风险，有利于我们在临床中用药时进行全面评估后再选择用药。

参考文献

[1] Liu, C., Lyu, H., Niu, P., Tan, J. and Ma, Y. (2020) Association between Diabetic Neuropathy and Osteoporosis in Patients: A Systematic Review and Meta-Analysis. *Archives of Osteoporosis*, **15**, Article No. 125. https://doi.org/10.1007/s11657-020-00804-6

[2] Lotfy, M., Adeghate, J., Kalasz, H., Singh, J. and Adeghate, E. (2017) Chronic Complications of Diabetes Mellitus: A Mini Review. *Current Diabetes Reviews*, **13**, 3-10. https://doi.org/10.2174/1573399812666151016101622

[3] Kolluru, G.K., Bir, S.C. and Kevil, C.G. (2012) Endothelial Dysfunction and Diabetes: Effects on Angiogenesis, Vascular Remodeling, and Wound Healing. *International Journal of Vascular Medicine*, **2012**, Article ID: 918267. https://doi.org/10.1155/2012/918267

[4] Hayyan, M., Hashim, M.A. and Al Nashef, I.M. (2016) Superoxide Ion: Generation and Chemical Implications. *Chemical Reviews*, **116**, 3029-3085. https://doi.org/10.1021/acs.chemrev.5b00407

[5] Saito, M., Fujii, K., Soshi, S., *et al*. (2006) Reductions in Degree of Mineralization and Enzymatic Collagen Cross-Links and Increases in Glycation-Induced Pentosidine in the Femoral Neck Cortex in Cases of Femoral Neck Fracture. *Osteoporosis International*, **17**, 986-995. https://doi.org/10.1007/s00198-006-0087-0

[6] Li, G., Xu, J. and Li, Z. (2012) Receptor for Advanced Glycation End Products Inhibits Proliferation in Osteoblast through Suppression of Wnt, PI3K and ERK Signaling. *Biochemical and Biophysical Research Communications*, **423**, 684-689. https://doi.org/10.1016/j.bbrc.2012.06.015

[7] Ding, K.H., Wang, Z.Z., Hamrick, M.W., *et al*. (2006) Disordered Osteoclast Formation in RAGE Deficient Mouse Establishes an Essential Role for RAGE in Diabetes Related Bone Loss. *Biochemical and Biophysical Research Communications*, **340**, 1091-1097. https://doi.org/10.1016/j.bbrc.2005.12.107

[8] Hein, G.E. (2006) Glycation Endproducts in Osteoporosis—Is There a Pathophysiologic Importance? *Clinica Chimica Acta*, **371**, 32-36. https://doi.org/10.1016/j.cca.2006.03.017

[9] Patel, R., Shervington, A., Pariente, J.A., *et al*. (2006) Mechanism of Exocrine Pancreatic Insufficiency in Streptozotocin-Induced Ype 1 Diabetes Mellitus. *Annals of the New York Academy of Sciences*, **1084**, 71-88. https://doi.org/10.1196/annals.1372.038

[10] Chen, H. and Li, J. (2018) Wang Q Associations between Bone-Alkaline Phosphatase and Bone Mineral Density in Adults with and without Diabetes. *Medicine*, **97**, Article ID: e0432. https://doi.org/10.1097/MD.0000000000010432

[11] Ala, M., Jafari, R.M. and Dehpour, A.R. (2020) Diabetes Mellitus and Osteoporosis Correlation: Challenges and Hopes. *Current Diabetes Reviews*, **16**, 984-1001. https://doi.org/10.2174/1573399816666200324152517

[12] Adler, R. A., *et al*. (2013) Glucocorticoid-Induced Osteoporosis. In: Marcus, R. *et al*., Eds., *Osteoporosis*, Academic Press, Cambridge, MA, 1191-1223. https://doi.org/10.1016/B978-0-12-415853-5.00049-2

[13] Darjani, A., Nickhah, N., Hedayati Emami, M.H., *et al*. (2017) Assessment of the Prevalence and Risk Factors Associated with GlucocorticoidInduced Diabetes Mellitus in Pemphigus Vulgaris Patients. *Acta Medica Iranica*, **55**, 375-380.

[14] Weinstein, R.S., Jilka, R.L., Parfitt, A.M. and Manolagas, S.C. (1998) Inhibition of Osteoblastogenesis and Promotion

of Apoptosis of Osteoblasts and Osteocytes Byglucocorticoids. Potential Mechanisms of Their Deleterious Effects on Bone. *Journal of Clinical Investigation*, **102**, 274-282. https://doi.org/10.1172/JCI2799

[15] Almeida, M., Han, L., Ambrogini, E., Weinstein, R.S. and Manolagas, S.C. (2011) Glucocorticoids and Tumor Necrosis Factor α Increase Oxidative Stress and Suppress Wnt Protein Signaling in Osteoblasts. *Journal of Biological Chemistry*, **286**, 44326-44335. https://doi.org/10.1074/jbc.M111.283481

[16] Jagpal, A., De, S.D., Singh, S.A. and Kirk, A. (2018) Is Tacrolimus More Likely to Induce Diabetes Mellitus Than Ciclosporin in Heart Transplant Patients? *Vessel Plus*, **2**, Article No. 24. https://doi.org/10.20517/2574-1209.2018.27

[17] Velleca, A., Kittleson, M., Patel, J., Rafiei, M., Osborne, A., Ngan, A., *et al*. (2013) Tacrolimus-Versus Cyclosporine-Induced Diabetes Leads to More Diabetic Complications after Heart Transplantation. *The Journal of Heart and Lung Transplantation*, **32**, S202. https://doi.org/10.1016/j.healun.2013.01.498

[18] Baran, D., Ashkar, J., Galin, I., Sandler, D., Segura, L., Courtney, M., *et al*. (2002) Tacrolimus and New Onset Diabetes Mellitus: The Effect of Steroid Weaning. *Transplantation Proceedings*, **34**, 1711-1712. https://doi.org/10.1016/S0041-1345(02)02993-7

[19] Li, Z., Sun, F., Zhang, Y., *et al*. (2015) Tacrolimus Induces Insulin Resistance and Increases the Glucose Absorption in the Jejunum: A Potential Mechanism of the Diabetogenic Effects. *PLoS ONE*, **10**, Article ID: e0143405. https://doi.org/10.1371/journal.pone.0143405

[20] Rodríguez-Rodríguez, A.E., Triñanes, J., Porrini, E., *et al*. (2015) Glucose Homeostasis Changes and Pancreatic *β*-Cell Proliferation after Switching to Cyclosporin in Tacrolimus-Induced Diabetes Mellitus. *Nefrologia*, **35**, 264-272. [English Edition]. https://doi.org/10.1016/j.nefroe.2015.06.006

[21] Triñanes, J., Rodriguez-Rodriguez, A.E., Brito-Casillas, Y., *et al*. (2017) Deciphering Tacrolimus-Induced Toxicity in Pancreatic *β* Cells. *American Journal of Transplantation*, **17**, 2829-2840. https://doi.org/10.1111/ajt.14323

[22] Sheu, A. and Diamond, T. (2016) Secondary Osteoporosis. *Australian Prescriber*, **39**, 85-87. https://doi.org/10.18773/austprescr.2016.020

[23] Spolidorio, L.C., Nassar, P.O., Nassar, C.A., Spolidorio, D.M. and Muscará, M.N. (2007) Conversion of Immunosuppressive Monotherapy from Cyclosporin A to Tacrolimus Reverses Bone Loss in Rats. *Calcified Tissue International*, **81**, 114-123. https://doi.org/10.1007/s00223-007-9040-2

[24] Ponticelli, C., Aroldi, A., Goffin, E., Devendra, D. and Wilkin, T. (2001) Osteoporosis after Organ Transplantation. *Lancet*, **357**, 1623. https://doi.org/10.1016/S0140-6736(00)04765-6

[25] Martin-Fernandez, M., Rubert, M., Montero, M. and De La Piedra, C. (2017) Effects of Cyclosporine, Tacrolimus, and Rapamycin on Osteoblasts *Transplantation Proceedings*, **49**, 2219-2224. https://doi.org/10.1016/j.transproceed.2017.07.005

[26] Smallwood, G., Burns, D., Fasola, C., Steiber, A. and Heffron, T. (2005) Relationship between Immunosuppression and Osteoporosis in an Outpatient Liver Transplant Clinic. *Transplantation Proceedings*, **37**, 1910-1911. https://doi.org/10.1016/j.transproceed.2005.02.078

[27] Goldner, M.G., Zarowitz, H. and Akgun, S. (1960) Hyperglycemia and Glycosuria Due to Thiazide Derivatives Administered in Diabetes Mellitus. *New England Journal of Medicine*, **262**, 403-405. https://doi.org/10.1056/NEJM196002252620807

[28] Scheen, A.J. (2018) Type 2 Diabetes and Thiazide Diuretics. *Current Diabetes Reports*, **18**, Article No. 6. https://doi.org/10.1007/s11892-018-0976-6

[29] Zillich, A.J., Garg, J., Basu, S., Bakris, G.L. and Carter, B.L. (2006) Thiazide Diuretics, Potassium, and the Development of Diabetes: A Quantitative Review. *Hypertension*, **48**, 219-224. https://doi.org/10.1161/01.HYP.0000231552.10054.aa

[30] Shafi, T., Appel, L.J., Miller III, E.R., Klag, M.J. and Parekh, R.S. (2008) Changes in Serum Potassium Mediate Thiazide-Induced Diabetes. *Hypertension*, **52**, 1022-1029. https://doi.org/10.1161/HYPERTENSIONAHA.108.119438

[31] Rapoport, M.I. and Hurd, H.F. (1964) Thiazide-Induced Glucose Intolerance Treated with Potassium. *Archives of Internal Medicine*, **113**, 405-408. https://doi.org/10.1001/archinte.1964.00280090091014

[32] Helderman, J.H., Elahi, D., Andersen, D.K., Raizes, G.S., Tobin, J.D., Shocken, D., *et al*. (1986) Prevention of the Glucose Intolerance of Thiazide Diuretics by Maintenance of Body-Potassium. In: Krück, F. and Schrey, A., Eds., *Diuretika III*, Springer, Berlin, Heidelberg, 98-109. https://doi.org/10.1007/978-3-642-71487-0_10

[33] Brown, M.J., Williams, B., Morant, S.V., *et al*. (2016) Effect of Amiloride, or Amiloride plus Hydrochlorothiazide, Versus Hydrochlorothiazide on Glucose Tolerance and Blood Pressure (PATHWAY-3): A Parallelgroup, Double-Blind Randomised Phase 4 Trial. *The Lancet Diabetes & Endocrinology*, **4**, 136-147. https://doi.org/10.1016/S2213-8587(15)00377-0

[34] Transbøl, I., Christensen, M.S., Jensen, G.F., Christiansen, C. and McNair, P. (1982) Thiazide for the Postponement of Postmenopausal Bone Loss. *Metabolism*, **31**, 383-386. https://doi.org/10.1016/0026-0495(82)90115-9

[35] Cauley, J.A., Cummings, S.R., Seeley, D.G., *et al*. (1993) Effects of Thiazide Diuretic Therapy on Bone Mass, Fractures, and Falls. *Annals of Internal Medicine*, **118**, 666-673. https://doi.org/10.7326/0003-4819-118-9-199305010-00002

[36] Xiao, X., Xu, Y. and Wu, Q. (2018) Thiazide Diuretic Usage and Risk of Fracture: A Meta-Analysis of Cohort Studies. *Osteoporosis International*, **29**, 1515-1524. https://doi.org/10.1007/s00198-018-4486-9

[37] Legroux-Gerot, I., Catanzariti, L., Marchandise, X., Duquesnoy, B. and Cortet, B. (2004) Bone Mineral Density Changes in Hypercalciuretic Osteo Porotic Men Treated with Thiazide Diuretics. *Joint Bone Spine*, **71**, 51-55. https://doi.org/10.1016/j.jbspin.2003.09.009

[38] Kruse, C., Eiken, P. and Vestergaard, P. (2016) Continuous and Long-Term Treatment Is More Important Than Dosage for the Protective Effect of Thiazide Use on Bone Metabolism and Fracture Risk. *Journal of Internal Medicine*, **279**, 110-122. https://doi.org/10.1111/joim.12397

[39] Cheng, L., Zhang, K. and Zhang, Z. (2018) Effectiveness of Thiazides on Serum and Urinary Calcium Levels and Bone Mineral Density in Patients with Osteoporosis: A Systematic Review and Meta-Analysis. *Drug Design, Development and Therapy*, **12**, 3929-3235. https://doi.org/10.2147/DDDT.S179568

[40] Mefford, I.N. and Wade, E.U. (2009) Proton Pump Inhibitors as a Treatment Method for Type II Diabetes. *Medical Hypotheses*, **73**, 29-32. https://doi.org/10.1016/j.mehy.2009.02.010

[41] Suarez-Pinzon, W.L., Cembrowski, G.S. and Rabinovitch, A. (2009) Combination Therapy with A Dipeptidyl Peptidase-4 Inhibitor and A Proton Pump Inhibitor Restores Normoglycaemia in Non-Obese Diabetic Mice. *Diabetologia*, **52**, 1680-1682. https://doi.org/10.1007/s00125-009-1390-z

[42] Crouch, M.A., Mefford, I.N. and Wade, E.U. (2012) Proton Pump Inhibitor Therapy Associated with Lower Glycosylated Hemoglobin Levels in Type 2 Diabetes. *Journal of the American Board of Family Medicine*, **25**, 50-54. https://doi.org/10.3122/jabfm.2012.01.100161

[43] Inci, F., Atmaca, M., Ozturk, M., *et al*. (2014) Pantoprazole May Improve Beta Cell Function and Diabetes Mellitus. *Journal of Endocrinological Investigation*, **37**, 449-454. https://doi.org/10.1007/s40618-013-0040-y

[44] Singh, P.K., Hota, D., Dutta, P., *et al*. (2012) Pantoprazole Improves Glycemic Control in Type 2 Diabetes: A Randomized, Double-Blind, Placebocontrolled Trial. *Journal of Clinical Endocrinology & Metabolism*, **97**, E2105-E2108. https://doi.org/10.1210/jc.2012-1720

[45] Lin, H.-C., Hsiao, Y.-T., Lin, H.-L., *et al*. (2016) The Use of Proton Pump Inhibitors Decreases the Risk of Diabetes Mellitus in Patients with Upper Gastrointestinal Disease: A Population-Based Retrospective Cohort Study. *Medicine*, **95**, E4195. https://doi.org/10.1097/MD.0000000000004195

[46] Suarez-Pinzon, W.L., Lakey, J.R. and Rabinovitch, A. (2008) Combination Therapy with Glucagon-Like Peptide-1 and Gastrin Induces β-Cell Neogenesis from Pancreatic Duct Cells in Human Islets Transplanted in Immunodeficient Diabetic Mice. *Cell Transplant*, **17**, 631-640. https://doi.org/10.3727/096368908786092775

[47] Suarez-Pinzon, W.L. and Rabinovitch, A. (2011) Combination Therapy with A Dipeptidyl Peptidase-4 Inhibitor and A Proton Pump Inhibitor Induces β-Cell Neogenesis from Adult Human Pancreatic Duct Cells Implanted in Immunodeficient Mice. *Cell Transplant*, **20**, 1343-1349. https://doi.org/10.3727/096368910X557263

[48] Abbasi, A., Corpeleijn, E., Postmus, D., *et al*. (2010) Plasma Procalcitonin Is Associated with Obesity, Insulin Resistance, and the Metabolic Syndrome. *Journal of Clinical Endocrinology & Metabolism*, **95**, E26-E31. https://doi.org/10.1210/jc.2010-0305

[49] Hjuler, S.T., Gydesen, S., Andreassen, K.V., Karsdal, M.A. and Henriksen, K. (2017) The Dual Amylin- and Calcitonin-Receptor Agonist KBP-042 Works as Adjunct to Metformin on Fasting Hyperglycemia and HbA1c in a Rat Model of Type 2 Diabetes. *Journal of Pharmacology and Experimental Therapeutics*, **362**, 24-30. https://doi.org/10.1124/jpet.117.241281

[50] Andreassen, K.V., Michael Feigh, M., Hjuler, S.T., Gydesen, S., Henriksen, J.E., Beck-Nielsen, H., *et al*. (2014) A Novel Oral Dual Amylin and Calcitonin Receptor Agonist (KBP-042) Exerts Anti-Obesity and Antidiabetic Effects in Rats. *American Journal of Physiology - Endocrinology and Metabolism*, **307**, E24-E33. https://doi.org/10.1152/ajpendo.00121.2014

[51] Binkley, N., Bolognese, M., Sidorowicz-Bialynicka, A., *et al*. (2012) A Phase 3 Trial of the Efficacy and Safety of Oral Recombinant Calcitonin: The Oral Calcitonin in Postmenopausal Osteoporosis (ORACAL) Trial. *Journal of Bone and Mineral Research*, **27**, 1821-1829. https://doi.org/10.1002/jbmr.1602

[52] Zhou, H. and Seibel, M.J. (2017) Bone: Osteoblasts and Global Energy Metabolism—Beyond Osteocalcin. *Nature Reviews Rheumatology*, **13**, 261-262. https://doi.org/10.1038/nrrheum.2017.35