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心血管疾病与糖尿病肾脏病之间的代谢关联

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摘　要

心血管疾病(cardiovascular disease, CVD)与糖尿病以及慢性肾脏病(chronic kidney disease, CKD)均是最常见的疾病。已有的流行病学研究与临床研究均有证据支持三者之间相互关联，并且定义了心脏–代谢–肾脏疾病CMR (cardio-metabolic-renal disease)这一概念。三者之间相互联系，相互影响，具有显著的流行病学、病理生理学和预后意义。既往研究发现高糖状态可以诱发心肾系统损害，然而三者之间如何影响以及影响的具体程度仍然存在争议，因此本综述主要概括了糖尿病，分别陈述了包括1型糖尿病、2型糖尿病与心血管之间的相互关联，并讨论了涉及肾脏病的部分。

关键词

代谢综合征，心脏代谢，1型糖尿病，2型糖尿病，肾脏病

Metabolic Associations between Cardiovascular Disease, Diabetes and Kidney Disease

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Abstract

Cardiovascular disease (CVD), diabetes and chronic kidney disease (CKD) are the most common diseases. The existing epidemiological research and clinical research all have evidence to support the

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correlation among them, and have defined the concept of CMR (cardiac-metabolic-renal disease). The three are interconnected and influence each other, holding significant epidemiological, pathophysiological, and prognostic implications. In previous studies, high glucose can induce damage to the heart and kidney system. However, how and to what extent it affects the heart and kidney system is still controversial. Therefore, this review mainly summarizes diabetes, respectively states the correlation between type 1 diabetes, type 2 diabetes and the cardiovascular system, and discusses the part involving kidney disease.

Keywords

Metabolic Syndrome, Cardiac Metabolism, Type 1 Diabetes, Type 2 Diabetes, Kidney Disease

1. 糖尿病与心血管疾病之间的现状研究

1.1. 1 型糖尿病(Type 1 Diabetes, T1D)与心血管疾病的关联研究并涉及尿蛋白

就目前研究而言，CVD 是 T1D 的常见并发症，也是导致死亡的主要原因。T1D 患者发生 CVD 事件的风险较高。有关于 3250 名 T1D 患者的横断面研究中表明，男性 CVD 患病率为 9%，女性为 10% [1]。同样有关于 T1D 患者的研究表明 T1D 男性的主要 CVD 的风险比为 3.6，女性为 7.7，两组的平均年龄为 33 岁[2]。可见 T1D 患者会在更小年龄时患 CVD，瑞典的一项关于 T1D 患者的研究显示，在 26~30 岁之间发生 T1D 的患者患 CVD 的风险增加 3.85 倍，在 10 岁之前发生 T1D 的患者患 CVD 的风险增加 11.44 倍[3]。

年轻 T1D 患者的动脉粥样硬化风险增加。有近期的研究发现，与年龄匹配的健康对照组相比，青少年 T1D 与较高的主动脉内膜中层厚度相关[4]，相关研究显示 T1D 儿童的内皮功能显著受损，表明他们患 CVD 的风险更高[5]。在最近一项针对 T1D 患病至少 10 年且未确诊 CVD 的成人的横断面研究中，其中 37.3%的患者出现冠状动脉钙化[6]。

常见的 CVD 危险因素，如吸烟、低密度脂蛋白胆固醇和高血压，会增加 T1D 患者患 CVD 疾病的风险。吸烟是 T1D 患者的一个重要危险因素。有研究，追踪了 604 名无 CVD 的 T1D 患者，在 25 年中，发现吸烟是心血管不良事件 MACE (HR: 1.92 [1.34~2.73])和 CVD (HR: 1.75 [1.30~2.37])的独立危险因素[7]。低密度胆固醇 LDL-C 是 T1D 患者 CVD 或 MACE 的独立危险因素[8]。有研究表明与 LDL-C 值低于 100 mg/dL 的患者相比，LDL-C 值在 100 至 129 mg/dl 之间的 T1D 患者患冠状动脉疾病的风险增加 1.8，LDL-C 值在 130 至 159 mg/dl 之间的患者增加 2.3，LDL-C 值等于或高于 160 mg/dl 的患者增加 3.0 [9]。血压升高也是 T1D 患者的一个重要 CVD 危险因素。事实上，收缩压已被证明是 MACE 中任何 CVD 的独立危险因素[8]。

相关实验表明，尿白蛋白排泄率是 MACE 的独立危险因素，并非糖尿病肾病与 CVD 的发生风险呈直接联系。有研究表明白蛋白排泄率是首次致死性或非致死性 CVD 事件的独立因素[10]。有数据显示，大量白蛋白尿(>200 μg/min)使 CVD 风险增加 1.52，与年龄、糖尿病发病年龄、糖化血红蛋白、糖尿病病程、吸烟、总胆固醇/高密度脂蛋白胆固醇比值、血压和 CVD 病史无关[11]。并且有研究发现，视网膜和肾脏疾病的共同存在也是与 CVD 相关的独立因素[12]。微量白蛋白尿已被证明与氧化应激、炎症和内皮功能障碍有关[13]。糖尿病肾病只能是促进动脉粥样硬化发展的生物疾病的一个特征，但微量白蛋白尿在

CVD 发展中的直接作用仍然是未能明确原因的问题。

1.2. 2 型糖尿病(Type 2 Diabetes, T2D)与血管疾病、肾脏疾病之间的关联

绝大多数患者(约 90%)的糖尿病都是 T2D [14]，T2D 不仅发生大血管和微血管的风险很高，发生心衰的风险也很高，甚至比发生动脉粥样硬化性心脏病的风险更高[15] [16]，然而，心力衰竭直到最近才成为 T2D 患者治疗干预的焦点。

1.2.1. T2D 与心力衰竭(Heart Failure, HF)的关系

有研究表明，T2D 是新发 HF (风险比[RR]，2.14 [95% CI 1.96~2.34])和复发性 HF (RR, 1.39 [95% CI 1.33~1.45])的重要危险因素，尤其是在年轻人中[11]。关于 HF 队列研究中，T2D 的患病率也高于一般人群，在所有 HF 患者中为 24%，在因心衰而住院患者中为 40%。在坎地沙坦降低心衰患者死亡率与发病率评估的相关研究中发现，在最初非糖尿病人群的 HF 患者中，TD2 的发病率为 28/1000 人年[17]，远高于一般人群[18]。但是需要更多的相关研究来证实 T2D 与 HF2 个疾病之间的双相联系以及基础机制。但是可以预知的是，两者疾病共存会引起临床患者的预后变差，糖尿病是心衰患者的队列研究中不良临床结局、心血管事件发病率与死亡率的预测指标[19] [20]。并且，在 65 岁及其以上年龄的 T2D 患者中，心衰事件的发生和死亡高出 10 倍[21]。

1.2.2. T2D 与缺血性心脏病的关系

缺血性心脏病是 T2D 另一种并发症。对来自 102 项研究的近 700,000 名患者荟萃分析发现，高收入国家的 T2D 患者患缺血性心脏病的可能性大约是非糖尿病患者的两倍[22]。此外，T2D 患者死于冠心病的风险增加了 2.31 倍。在全球范围内，T2D 患者冠状动脉疾病的发病率因国家而异[23]-[25]；一些研究表明，亚洲国家的 T2D 患者发生主要冠状动脉事件的风险低于欧洲患者。

1.2.3. 2 型糖尿病与 CKD 的关系

在全球范围内，估计高达 50%的 T2D 患者还患有 CKD，定义为持续性白蛋白尿(尿白蛋白与肌酐比值 ≥30 mg/g)，估计肾小球滤过率(eGFR)持续低于 60 ml/min/1.73m^2 和/或两者[26]。在美国与日本的相关性研究中发现，蛋白尿和 eGFR 降低(<60 ml/min/1.73m)使 T2D 患者的死亡风险增加到相似程度，并且在蛋白尿合并 eGFR 降低的患者中进一步翻倍。并且研究发现，T2D 患者患 CKD 的风险存在人种差异[27]-[29]，在大型横断面研究中发现，微量白蛋白尿和大量白蛋白尿的患病率分别为 39%和 9.8%，其中亚洲人的白蛋白尿总体患病率最高[30]。这种差异与遗传因素、宫内环境、及公众意识、经济因素相关。尽管亚洲的糖尿病患病率显着增加，但许多亚洲患者缺乏意识，其中很大一部分人未被诊断出来。在糖尿病早期，肾小球发生高滤过现象[31]，在 40%的 T2D 患者中观察到这种现象，在糖尿病早期，由于近端小管的增生和肥大，导致肾小球滤过的重吸收增加，反馈到肾小球从而使 GFR 增加。持续的高滤过导致肾单位进行性和不可逆的损伤，eGFR 下降，最终终止于 ESKD。肾组织损伤表现为白蛋白尿和蛋白尿，这与代谢失调所导致的细胞功能和结构改变有关[32]。

糖尿病肾病中发生的肾小球结构变化包括肾小球基底膜厚度增加、足突融合、足细胞丢失和系膜基质扩张[33]。在后期，肾小管细胞萎缩，其功能障碍导致蛋白质再摄取受损和白蛋白尿[34]，肾小管间质纤维化是 DKD 进行性肾功能损害的最终共同途径[33]。

2. CVD 与 CKD 的关系

一项涉及约 110 万名心力衰竭患者的荟萃分析发现，总体 CKD 患病率为 49%，急性心力衰竭患者(53%)高于慢性心力衰竭患者(42%)。并且 CVD (包括心力衰竭)在 CKD 患者中比在一般人群中更普遍，

并且其患病率随着肾功能的下降而增加[35]。并且有研究表明 CKD 患者患心力衰竭的风险是非 CKD 患者两倍[36]。而 HOPE 等人研究发现[37]，微量白蛋白尿的存在使因心力衰竭住院的风险大约增加了一倍。在相关研究中，CKD 患者的主要不良心血管事件(心力衰竭、心肌梗死、中风)发生率为 38/1000 人年，而仅心肌梗死的发生率为 13/1000 人年[38]。在 CKD-JAC 研究中，CKD 患者的 CVD 发生率为 22.8/1000 人年，而心肌梗死的发生率为 1.6/1000 人年[39]。

有广泛的证据表明肾脏和心脏病之间存在密切的联系：心肾综合征(cardiorenal syndrome, CRS)一词被定义用来强调心肾相互作用的双向性，一个器官的急性或慢性功能障碍导致另一个器官的急性或慢性功能障碍[40]。血流动力学和神经激素异常可能是衰竭心脏和衰竭肾脏之间有害联系的关键因素[41]。HF 相关的低心输出量、有效低血容量和血管收缩介质过多导致慢性肾灌注不足和 eGFR 降低，有利于 CKD 的发生和进展[40]。并且，CKD 中的钠和水潴留以及慢性 RAAS 激活会加剧高血压并增加心脏前负荷和后负荷。这些血流动力学异常以及 CKD 相关的尿毒症毒素潴留和慢性炎症促使病理性心脏重塑和心功能障碍的发生和恶化，共同对心肾器官产生有害的恶性循环[40]。

3. 高糖状态与心血管疾病、肾脏病之间病理关联机制

高糖状态与心血管疾病的现状研究

长期高糖状态是与 T1D 动脉粥样硬化相关的主要因素，有研究表明，HbA1c 每增加 1%，MACE 增加 42% [8]，在关于 T1D 患者 30 年的随访研究中，将人群分为低 HbA1c 组，平均 HbA1c 为 8.4%，在随访期间改善至 7.7%，高 HbA1c 组，平均 HbA1c 为 10%，在随访期间维持，发现与低 HbA1c 组相比，高 HbA1c 组患者的 CVD 风险增加了 3 倍[42]。在低 HbA1c 组患者中，非 HDL-C、肾小球滤过率和吸烟与 CVD 总风险密切相关，而在高 HbA1c 组的患者中，高血压和白蛋白尿占主导地位[42]。在糖尿病病程超过 50 年的 T1D 患者中，HbA1c 增加 1%与 CVD 事件风险增加 26%相关[43]。此外，胰腺移植后 T1D 患者冠状动脉粥样硬化病变、CVD 和冠状动脉死亡率显著降低，支持高血糖在 T1D 动脉粥样硬化发病机制中的重要作用[44]。

高糖状态与心血管疾病的病理生理学机制

高糖状态会导致甘油二酰基甘油(DAG)、蛋白激酶 C (PKC)激活，导致多种生化修饰，PKC 激活后会导致一氧化氮的产生减少从而使血管收缩[45]。此外还会促进活性氧(ROS)的形成，从而对血管壁产生负面影响[46]。高糖状态还可通过激活多元醇途径，促进细胞内的氧化应激，对动脉壁产生有害影响[45]。慢性高糖状态还会诱导蛋白质的非酶促糖基化，导致晚期糖基化终末产物(AGE)的形成，这些终末产物通过特异性受体(RAGE)与动脉壁相互作用，在内皮细胞中表达。AGE/RAGE 相互作用作用于内皮细胞，通过 NF-κB 激活和 ROS 的形成促进炎症[47] [48]。AGEs 可直接导致细胞外基质中的胶原蛋白和层粘连蛋白等蛋白质交联，导致血管硬化[49]。此外，这些影响被认为部分是糖尿病心肌病病理生理学的基础[50]和糖尿病肾病[51]。此外 AGEs 的主要前体甲基乙二醛(AGEs 的主要前体)已被证明与人类颈动脉破裂易发斑块有关[48]，并且在一项针对 T1D 患者的 12 年随访研究中，AGEs 是 CVD 事件的独立因素[52]。此外，戊糖素(一种 AGE)的血浆水平与 T1D 患者的冠状动脉钙化有关[53]。

单纯的高糖状态并不能解释一些导致相关的心血管疾病因素，所以本文将从 T1D 患者和 T2D 患者分别进一步阐述导致 CVD 风险增加的因素。

4. T1D 患者 CVD 风险增高还可能涉及几个其他因素

4.1. 低血糖

一项回顾性研究发现无 CVD 病史的 T1D 患者发生低血糖与 CVD 事件风险增加显著相关[54]。另一

项回顾性研究纳入了 1550 例接受胰岛素泵治疗的 T1D 患者，发现重度低血糖是 CVD 的独立危险因素[55]。解释低血糖与 CVD 风险之间的病理生理机制尚未完全阐明。反复发作低血糖的 T1D 患者显示出 NO 介导的内皮血管舒张减少[56]。在健康受试者和 T1D 患者中，低血糖期间粘附分子(VCAM-1、ICAM-1、E-选择素)和促炎分子(TNF-α 和 IL-6)水平增加[57]。此外，在健康受试者和 T1D 患者中，由高胰岛素－低血糖钳夹诱导的低血糖增加了血小板活化标志物(P-选择素)和 PAI-1 (表明纤维蛋白溶解减少) [58]。

4.2. 血糖变异性

血糖变异性增加可能是促进 T1D 发生 CVD 的一个因素。已发现血糖变异性增加非糖尿病个体的 CVD [59]。并且和 T2D 患者的冠状动脉疾病严重程度独立相关[60]。一些研究表明，血糖变异性会增强促炎细胞因子的释放和氧化应激[61]。T2D 患者，血糖变异性被证明会促进内皮功能障碍[62]。尽管一些数据表明血糖变异性增加可能会促进 T1D 患者的 CVD，但这需要通过进一步的研究来证实。

4.3. 超重或肥胖引起的胰岛素抵抗

T1D 患者超重和肥胖的患病率不断增加[63]。超重/肥胖的 T1D 患者经常具有代谢综合征的特征，例如腹部肥胖、低 HDL-C 和血浆甘油三酯升高[64] [65]。与其他 T1D 患者相比，患有代谢综合征的 T1D 患者的 CVD 风险更高[64] [66]。与超重 T1D 患者相关的胰岛素抵抗可通过不同的机制促进 CVD，例如内脏脂肪增加、甘油三酯增加、低 HDL-胆固醇、低度炎症、纤维蛋白溶解减少类似于 T2D [67]。

4.4. 脂代谢紊乱

在血糖控制不佳的 T1D 患者中，可以发现血浆甘油三酯和低密度脂蛋白胆固醇水平升高[68]。在所有 T1D 患者，即使血糖控制良好，也表现出脂蛋白的多种定性和功能异常，这些异常可能引起动脉粥样硬化[69]。T1D 中脂蛋白组成的改变被认为是由胆固醇酯转移蛋白(CETP)活性增加引起的，这可能是由皮下注射胰岛素方法引起的外周高胰岛素血症引起的[70]。此外，来自糖尿病控制良好的 T1D 患者的 VLDL 和 LDL 颗粒的游离胆固醇/卵磷脂比率在脂蛋白外围增加，这可能会降低它们的流动性和稳定性。已经证明，在 T1D 患者中，HDL 刺激巨噬细胞胆固醇外流的能力大大降低，这与血糖控制无关[71]。与血糖控制水平无关，1 型糖尿病患者去除和降低与 LDL 或细胞膜相关的脂质氢过氧化物的能力持续降低，这可能是由于 HDL 相关对氧磷酶-1 (PON1)活性降低[72]。此外，T1D 患者已经失去了 HDL 的内皮依赖性血管松弛作用[73]。这可能是在 T1D 患者中观察到的 1-磷酸鞘氨醇(S1P)减少的结果，因为 HDL-S1P 刺激内皮产生 NO [74]。

4.5. 免疫反应功能失调

英国最近在 446,449 名自身免疫性疾病患者和 2,102,830 名匹配对照组中进行的人群研究一致，中位随访时间为 6.2 年，结果显示自身免疫性疾病患者的 CVD 风险增加(HR = 1 × 56 [1 × 52 − 1 × 59]) [75]。根据某些研究，自身免疫性 T1D 的典型免疫系统功能障碍也可能促进 CVD 疾病[76] [77]。(免疫相关途径研究并不清楚，只有后面举例的研究支持此观点)心肌梗死后，83%的 T1D 患者检测到肌球蛋白自身抗体，但仅在 15%的 T2D 患者中检测到肌球蛋白自身抗体[76]。在 DCCT/EDIC 试验中，16%的 T1D 患者存在心脏抗体(与总肌球蛋白重链-α 或-β、α-肌球蛋白重链片段或肌钙蛋白相关)主要发生在血糖控制不佳的患者中[78]。此外，在 DCCT/EDIC 试验中，2 个或更多心脏自身抗体的阳性是可检测到 CAC 的独立因素[77]。这些发现支持免疫功能受损(可能通过炎症途径)可能会加速动脉粥样硬化发展的理论，尤其是在控制不佳的 T1D 患者中。

5. T2D 患者 CVD 风险增高还可能涉及几个其他因素

5.1. 胰岛素抵抗与脂代谢毒性

胰岛素代谢信号受损与心脏纤维化/僵硬和舒张功能障碍有关，已经提到心脏胰岛素抵抗被认为是糖尿病心肌病的主要病理生理学异常[49]。根据 T2D 中的研究，胰岛素抵抗与细胞代谢向游离脂肪酸(FFA)氧化的转变有关。游离脂肪酸(FFA)氧化比葡萄糖氧化更耗氧。这会导致代谢灵活性受损和能量效率降低[79] [80]。在 T2D 中，在以胰岛素依赖性方式吸收葡萄糖的细胞中，由于胰岛素抵抗导致的细胞内葡萄糖水平降低，可能会将代谢转向游离脂肪酸氧化，这是一种效率较低的过程。在糖尿病心脏中，葡萄糖代谢产生的三磷酸腺苷(ATP)减少可能导致游离脂肪酸摄取和三酰甘油积累的代偿性增加，这可能超过线粒体呼吸能力，导致有毒脂质代谢物的积累和线粒体功能障碍，进氧化应激、脂毒性和细胞凋亡[81]。心外膜脂肪组织(EAT)是位于心肌和心外膜之间的内脏脂肪库，具有调节心肌和冠状动脉的旁分泌特性[82]，已被提议作为缓冲器，为心肌提供能量，同时保护其免受 FFA 超负荷[83]。T2D 与 EAT 体积[84]细胞因子分泌谱和 FFA 释放的病理变化有关，这些变化是糖尿病相关心血管功能障碍的潜在驱动因素，例如动脉粥样硬化、心肌内脂肪浸润、心脏重塑和 HF [85]。在肾足细胞中，胰岛素受体信号传导缺陷也会导致让人想起糖尿病肾病的病理，即使血糖正常也是如此。

5.2. T2D 危害骨髓来源的造血干细胞/祖细胞(HSPC)

有已知研究表明 T2D 与循环 HSPC 水平降低有关[86]，主要是由于骨髓(BM)活动受损[87]。HSPC 缺陷与 T2D 人群中微血管和大血管并发症的发生广泛相关[88]，并且是不良心血管结局和死亡的危险因素[89]。BM 来源的细胞有助于损伤后肾实质再生的证据[90]可能表明 HSPC 缺乏在 DKD 中起作用。HSPCs 可能与非白蛋白尿性 DKD 特别相关，因为 HSPCs 与这种 CKD 表型发展中涉及的几个 CVD 危险因素之间存在关联[91]。根据这种观点，糖尿病可以被认为是一种损伤控制受损的疾病，存在组织修复的生理过程缺陷[92]。

6. 讨论

心血管疾病、糖尿病与肾脏疾病在病理生理学水平上相互作用，在临床上相互重叠、相互影响，一种疾病的发作会增加其他疾病的发生风险以及影响预后，这几种疾病之间形成恶性循环。认识心血管疾病、糖尿病与肾脏疾病之间的联系有助于早期识别和治疗高危患者，为疾病的诊断和管理和预防提出新策略，了解疾病的病理生理学机制有助于评估药物的治疗靶点，以及指导药物之间的联合使用，从而指导临床治疗，改善疾病结局。

参考文献

[1] Koivisto, V.A., Stevens, I.K., Mattock, M., Ebeling, P., Muggeo, M., Stephenson, J., *et al*. (1996) Cardiovascular Disease and Its Risk Factors in IDDM in Europe. *Diabetes Care*, **19**, 689-697. https://doi.org/10.2337/diacare.19.7.689

[2] Soedamah-Muthu, S.S., Fuller, J.H., Mulnier, H.E., Raleigh, V.S., Lawrenson, R.A. and Colhoun, H.M. (2006) High Risk of Cardiovascular Disease in Patients with Type 1 Diabetes in the UK: A Cohort Study Using the General Practice Research Database. *Diabetes Care*, **29**, 798-804. https://doi.org/10.2337/diacare.29.04.06.dc05-1433

[3] Rawshani, A., Sattar, N., Franzén, S., Rawshani, A., Hattersley, A.T., Svensson, A., *et al*. (2018) Excess Mortality and Cardiovascular Disease in Young Adults with Type 1 Diabetes in Relation to Age at Onset: A Nationwide, Register-Based Cohort Study. *The Lancet*, **392**, 477-486. https://doi.org/10.1016/s0140-6736(18)31506-x

[4] Gow, M.L., Varley, B.J., Nasir, R.F., Skilton, M.R. and Craig, M.E. (2022) Aortic Intima Media Thickness in Children and Adolescents with Type 1 Diabetes: A Systematic Review. *Pediatric Diabetes*, **23**, 489-498. https://doi.org/10.1111/pedi.13322

[5] Cao, L., Hou, M., Zhou, W., Sun, L., Shen, J., Chen, Y., *et al*. (2021) Decreased Flow-Mediated Dilatation in Children with Type 1 Diabetes: A Systematic Review and Meta-Analysis. *Angiology*, **72**, 908-915. https://doi.org/10.1177/00033197211010096

[6] Helleputte, S., Van Bortel, L., Verbeke, F., Opt Roodt, J., Calders, P., Lapauw, B., *et al*. (2022) Arterial Stiffness in Patients with Type 1 Diabetes and Its Comparison to Cardiovascular Risk Evaluation Tools. *Cardiovascular Diabetology*, **21**, Article No. 97. https://doi.org/10.1186/s12933-022-01537-1

[7] Miller, R.G., Costacou, T. and Orchard, T.J. (2018) Risk Factor Modeling for Cardiovascular Disease in Type 1 Diabetes in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study: A Comparison with the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC). *Diabetes*, **68**, 409-419. https://doi.org/10.2337/db18-0515

[8] Lachin, J.M. (2016) Risk Factors for Cardiovascular Disease in Type 1 Diabetes. *Diabetes*, **65**, 1370-1379. https://doi.org/10.2337/db15-1517

[9] Orchard, T.J., Forrest, K.Y., Kuller, L.H. and Becker, D.J. (2001) Lipid and Blood Pressure Treatment Goals for Type 1 Diabetes: 10-Year Incidence Data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care*, **24**, 1053-1059. https://doi.org/10.2337/diacare.24.6.1053

[10] Vistisen, D., Andersen, G.S., Hansen, C.S., Hulman, A., Henriksen, J.E., Bech-Nielsen, H., *et al*. (2016) Prediction of First Cardiovascular Disease Event in Type 1 Diabetes Mellitus: The Steno Type 1 Risk Engine. *Circulation*, **133**, 1058-1066. https://doi.org/10.1161/circulationaha.115.018844

[11] Cederholm, J., Eeg-Olofsson, K., Eliasson, B., Zethelius, B. and Gudbjörnsdottir, S. (2011) A New Model for 5-Year Risk of Cardiovascular Disease in Type 1 Diabetes; From the Swedish National Diabetes Register (NDR). *Diabetic Medicine*, **28**, 1213-1220. https://doi.org/10.1111/j.1464-5491.2011.03342.x

[12] Gubitosi-Klug, R., Gao, X., Pop-Busui, R., de Boer, I.H., White, N., Aiello, L.P., *et al*. (2021) Associations of Microvascular Complications with the Risk of Cardiovascular Disease in Type 1 Diabetes. *Diabetes Care*, **44**, 1499-1505. https://doi.org/10.2337/dc20-3104

[13] Orchard, T.J. and Costacou, T. (2016) Cardiovascular Complications of Type 1 Diabetes: Update on the Renal Link. *Acta Diabetologica*, **54**, 325-334. https://doi.org/10.1007/s00592-016-0949-7

[14] Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B.B., *et al*. (2022) IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045. *Diabetes Research and Clinical Practice*, **183**, Article ID: 109119. https://doi.org/10.1016/j.diabres.2021.109119

[15] Kodama, S., Fujihara, K., Horikawa, C., Sato, T., Iwanaga, M., Yamada, T., *et al*. (2020) Diabetes Mellitus and Risk of New-Onset and Recurrent Heart Failure: A Systematic Review and Meta-Analysis. *ESC Heart Failure*, **7**, 2146-2174. https://doi.org/10.1002/ehf2.12782

[16] Juhaeri, J., Gao, S. and Dai, W.S. (2009) Incidence Rates of Heart Failure, Stroke, and Acute Myocardial Infarction among Type 2 Diabetic Patients Using Insulin Glargine and Other Insulin. *Pharmacoepidemiology and Drug Safety*, **18**, 497-503. https://doi.org/10.1002/pds.1741

[17] Preiss, D., Zetterstrand, S., McMurray, J.J.V., Östergren, J., Michelson, E.L., Granger, C.B., *et al*. (2009) Predictors of Development of Diabetes in Patients with Chronic Heart Failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Diabetes Care*, **32**, 915-920. https://doi.org/10.2337/dc08-1709

[18] Geiss, L.S., Wang, J., Cheng, Y.J., Thompson, T.J., Barker, L., Li, Y., *et al*. (2014) Prevalence and Incidence Trends for Diagnosed Diabetes among Adults Aged 20 to 79 Years, United States, 1980-2012. *JAMA*, **312**, 1218-1226. https://doi.org/10.1001/jama.2014.11494

[19] MacDonald, M.R., Petrie, M.C., Varyani, F., Ostergren, J., Michelson, E.L., Young, J.B., *et al*. (2008) Impact of Diabetes on Outcomes in Patients with Low and Preserved Ejection Fraction Heart Failure: An Analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Programme. *European Heart Journal*, **29**, 1377-1385. https://doi.org/10.1093/eurheartj/ehn153

[20] Shindler, D.M., Kostis, J.B., Yusuf, S., Quinones, M.A., Pitt, B., Stewart, D., *et al*. (1996) Diabetes Mellitus, a Predictor of Morbidity and Mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *The American Journal of Cardiology*, **77**, 1017-1020. https://doi.org/10.1016/s0002-9149(97)89163-1

[21] Bertoni, A.G., Hundley, W.G., Massing, M.W., Bonds, D.E., Burke, G.L. and Goff, D.C. (2004) Heart Failure Prevalence, Incidence, and Mortality in the Elderly with Diabetes. *Diabetes Care*, **27**, 699-703. https://doi.org/10.2337/diacare.27.3.699

[22] The Emerging Risk Factors Collaboration, (2010) Diabetes Mellitus, Fasting Blood Glucose Concentration, and Risk of Vascular Disease: A Collaborative Meta-Analysis of 102 Prospective Studies. *The Lancet*, **375**, 2215-2222. https://doi.org/10.1016/s0140-6736(10)60484-9

[23] Cui, Y., Hao, K., Takahashi, J., Miyata, S., Shindo, T., Nishimiya, K., *et al*. (2017) Age-Specific Trends in the Incidence and In-Hospital Mortality of Acute Myocardial Infarction over 30 Years in Japan—Report from the Miyagi AMI Registry Study. *Circulation Journal*, **81**, 520-528. https://doi.org/10.1253/circj.cj-16-0799

[24] Harding, J.L., Pavkov, M.E., Magliano, D.J., Shaw, J.E. and Gregg, E.W. (2018) Global Trends in Diabetes Complications: A Review of Current Evidence. *Diabetologia*, **62**, 3-16. https://doi.org/10.1007/s00125-018-4711-2

[25] Gregg, E.W., Li, Y., Wang, J., Rios Burrows, N., Ali, M.K., Rolka, D., *et al*. (2014) Changes in Diabetes-Related Complications in the United States, 1990-2010. *New England Journal of Medicine*, **370**, 1514-1523. https://doi.org/10.1056/nejmoa1310799

[26] Khunti, K., Charbonnel, B., Chen, H., Cherney, D.Z., Cooper, A., Fenici, P., *et al*. (2021) Prevalence and Progression of Chronic Kidney Disease among Patients with Type 2 Diabetes: Insights from the Discover Study. *Diabetes, Obesity and Metabolism*, **23**, 1956-1960. https://doi.org/10.1111/dom.14401

[27] Chi, Z.S., Lee, E.T., Lu, M., Keen, H. and Bennett, P.H. (2001) Vascular Disease Prevalence in Diabetic Patients in China: Standardised Comparison with the 14 Centres in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*, **44**, S82-S86. https://doi.org/10.1007/pl00002944

[28] Lee, E.T., Keen, H., Bennett, P.H., Fuller, J.H. and Lu, M. (2001) Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: General Description and Morbidity. *Diabetologia*, **44**, S3-S13. https://doi.org/10.1007/pl00002936

[29] Lee, E.T., Lu, M., Bennett, P.H. and Keen, H. (2001) Vascular Disease in Younger-Onset Diabetes: Comparison of European, Asian and American Indian Cohorts of the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*, **44**, S78-S81. https://doi.org/10.1007/pl00002943

[30] Parving, H., Lewis, J.B., Ravid, M., Remuzzi, G. and Hunsicker, L.G. (2006) Prevalence and Risk Factors for Microalbuminuria in a Referred Cohort of Type II Diabetic Patients: A Global Perspective. *Kidney International*, **69**, 2057-2063. https://doi.org/10.1038/sj.ki.5000377

[31] Premaratne, E., Verma, S., Ekinci, E.I., Theverkalam, G., Jerums, G. and MacIsaac, R.J. (2015) The Impact of Hyperfiltration on the Diabetic Kidney. *Diabetes & Metabolism*, **41**, 5-17. https://doi.org/10.1016/j.diabet.2014.10.003

[32] Jefferson, J.A., Shankland, S.J. and Pichler, R.H. (2008) Proteinuria in Diabetic Kidney Disease: A Mechanistic Viewpoint. *Kidney International*, **74**, 22-36. https://doi.org/10.1038/ki.2008.128

[33] Thomas, M.C., Brownlee, M., Susztak, K., Sharma, K., Jandeleit-Dahm, K.A.M., Zoungas, S., *et al*. (2015) Correction: Diabetic Kidney Disease. *Nature Reviews Disease Primers*, **1**, Article No. 15018. https://doi.org/10.1038/nrdp.2015.70

[34] Vallon, V. (2011) The Proximal Tubule in the Pathophysiology of the Diabetic Kidney. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **300**, R1009-R1022. https://doi.org/10.1152/ajpregu.00809.2010

[35] Jankowski, J., Floege, J., Fliser, D., Böhm, M. and Marx, N. (2021) Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. *Circulation*, **143**, 1157-1172. https://doi.org/10.1161/circulationaha.120.050686

[36] Levey, A.S., de Jong, P.E., Coresh, J., El Nahas, M., Astor, B.C., Matsushita, K., *et al*. (2011) The Definition, Classification, and Prognosis of Chronic Kidney Disease: A KDIGO Controversies Conference Report. *Kidney International*, **80**, 17-28. https://doi.org/10.1038/ki.2010.483

[37] Kottgen, A., Russell, S.D., Loehr, L.R., Crainiceanu, C.M., Rosamond, W.D., Chang, P.P., *et al*. (2007) Reduced Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study. *Journal of the American Society of Nephrology*, **18**, 1307-1315. https://doi.org/10.1681/asn.2006101159

[38] Denker, M., Boyle, S., Anderson, A.H., Appel, L.J., Chen, J., Fink, J.C., *et al*. (2015) Chronic Renal Insufficiency Cohort Study (CRIC): Overview and Summary of Selected Findings. *Clinical Journal of the American Society of Nephrology*, **10**, 2073-2083. https://doi.org/10.2215/cjn.04260415

[39] Tanaka, K., Watanabe, T., Takeuchi, A., Ohashi, Y., Nitta, K., Akizawa, T., *et al*. (2017) Cardiovascular Events and Death in Japanese Patients with Chronic Kidney Disease. *Kidney International*, **91**, 227-234. https://doi.org/10.1016/j.kint.2016.09.015

[40] Ronco, C., Haapio, M., House, A.A., Anavekar, N. and Bellomo, R. (2008) Cardiorenal Syndrome. *Journal of the American College of Cardiology*, **52**, 1527-1539. https://doi.org/10.1016/j.jacc.2008.07.051

[41] Braam, B., Joles, J.A., Danishwar, A.H. and Gaillard, C.A. (2013) Cardiorenal Syndrome—Current Understanding and Future Perspectives. *Nature Reviews Nephrology*, **10**, 48-55. https://doi.org/10.1038/nrneph.2013.250

[42] Miller, R.G., Orchard, T.J. and Costacou, T. (2021) 30-year Cardiovascular Disease in Type 1 Diabetes: Risk and Risk Factors Differ by Long-Term Patterns of Glycemic Control. *Diabetes Care*, **45**, 142-150. https://doi.org/10.2337/dc21-1381

[43] Harjutsalo, V., Barlovic, D.P., Gordin, D., Forsblom, C., King, G. and Groop, P. (2021) Presence and Determinants of

Cardiovascular Disease and Mortality in Individuals with Type 1 Diabetes of Long Duration: The Finndiane 50 Years of Diabetes Study. *Diabetes Care*, **44**, 1885-1893. https://doi.org/10.2337/dc20-2816

[44] Senior, P.A. (2021) Glucose as a Modifiable Cause of Atherosclerotic Cardiovascular Disease: Insights from Type 1 Diabetes and Transplantation. *Atherosclerosis*, **335**, 16-22. https://doi.org/10.1016/j.atherosclerosis.2021.09.001

[45] Brownlee, M. (2001) Biochemistry and Molecular Cell Biology of Diabetic Complications. *Nature*, **414**, 813-820. https://doi.org/10.1038/414813a

[46] Koike, N., Takamura, T. and Kaneko, S. (2007) Induction of Reactive Oxygen Species from Isolated Rat Glomeruli by Protein Kinase C Activation and TNF-α Stimulation, and Effects of a Phosphodiesterase Inhibitor. *Life Sciences*, **80**, 1721-1728. https://doi.org/10.1016/j.lfs.2007.02.001

[47] Vlassara, H., Fuh, H., Makita, Z., Krungkrai, S., Cerami, A. and Bucala, R. (1992) Exogenous Advanced Glycosylation End Products Induce Complex Vascular Dysfunction in Normal Animals: A Model for Diabetic and Aging Complications. *Proceedings of the National Academy of Sciences*, **89**, 12043-12047. https://doi.org/10.1073/pnas.89.24.12043

[48] Schleicher, E. and Friess, U. (2007) Oxidative Stress, AGE, and Atherosclerosis. *Kidney International*, **72**, S17-S26. https://doi.org/10.1038/sj.ki.5002382

[49] Forbes, J.M. and Cooper, M.E. (2013) Mechanisms of Diabetic Complications. *Physiological Reviews*, **93**, 137-188. https://doi.org/10.1152/physrev.00045.2011

[50] Jia, G., DeMarco, V.G. and Sowers, J.R. (2015) Insulin Resistance and Hyperinsulinaemia in Diabetic Cardiomyopathy. *Nature Reviews Endocrinology*, **12**, 144-153. https://doi.org/10.1038/nrendo.2015.216

[51] Yamamoto, Y., Kato, I., Doi, T., Yonekura, H., Ohashi, S., Takeuchi, M., *et al*. (2001) Development and Prevention of Advanced Diabetic Nephropathy in Rage-Overexpressing Mice. *Journal of Clinical Investigation*, **108**, 261-268. https://doi.org/10.1172/jci11771

[52] Hanssen, N.M.J., Scheijen, J.L.J.M., Jorsal, A., Parving, H., Tarnow, L., Rossing, P., *et al*. (2017) Higher Plasma Methylglyoxal Levels Are Associated with Incident Cardiovascular Disease in Individuals with Type 1 Diabetes: A 12-Year Follow-Up Study. *Diabetes*, **66**, 2278-2283. https://doi.org/10.2337/db16-1578

[53] van Eupen, M.G., Schram, M.T., Colhoun, H.M., Scheijen, J.L., Stehouwer, C.D. and Schalkwijk, C.G. (2013) Plasma Levels of Advanced Glycation Endproducts Are Associated with Type 1 Diabetes and Coronary Artery Calcification. *Cardiovascular Diabetology*, **12**, Article No. 149. https://doi.org/10.1186/1475-2840-12-149

[54] Khunti, K., Davies, M., Majeed, A., Thorsted, B.L., Wolden, M.L. and Paul, S.K. (2014) Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People with Type 1 and Type 2 Diabetes: A Cohort Study. *Diabetes Care*, **38**, 316-322. https://doi.org/10.2337/dc14-0920

[55] Giménez, M., López, J.J., Castell, C. and Conget, I. (2012) Hypoglycaemia and Cardiovascular Disease in Type 1 Diabetes. Results from the Catalan National Public Health Registry on Insulin Pump Therapy. *Diabetes Research and Clinical Practice*, **96**, e23-e25. https://doi.org/10.1016/j.diabres.2012.01.014

[56] Giménez, M., Gilabert, R., Monteagudo, J., Alonso, A., Casamitjana, R., Paré, C., *et al*. (2010) Repeated Episodes of Hypoglycemia as a Potential Aggravating Factor for Preclinical Atherosclerosis in Subjects with Type 1 Diabetes. *Diabetes Care*, **34**, 198-203. https://doi.org/10.2337/dc10-1371

[57] Gogitidze Joy, N., Hedrington, M.S., Briscoe, V.J., Tate, D.B., Ertl, A.C. and Davis, S.N. (2010) Effects of Acute Hypoglycemia on Inflammatory and Pro-Atherothrombotic Biomarkers in Individuals with Type 1 Diabetes and Healthy Individuals. *Diabetes Care*, **33**, 1529-1535. https://doi.org/10.2337/dc09-0354

[58] Joy, N.G., Tate, D.B., Younk, L.M. and Davis, S.N. (2015) Effects of Acute and Antecedent Hypoglycemia on Endothelial Function and Markers of Atherothrombotic Balance in Healthy Humans. *Diabetes*, **64**, 2571-2580. https://doi.org/10.2337/db14-1729

[59] Yu, J.H., Han, K., Park, S., Lee, D.Y., Nam, G.E., Seo, J.A., *et al*. (2019) Effects of Long-Term Glycemic Variability on Incident Cardiovascular Disease and Mortality in Subjects without Diabetes: A Nationwide Population-Based Study. *Medicine*, **98**, e16317. https://doi.org/10.1097/md.0000000000016317

[60] Benalia, M., Zeller, M., Mouhat, B., Guenancia, C., Yameogo, V., Greco, C., *et al*. (2019) Glycaemic Variability Is Associated with Severity of Coronary Artery Disease in Patients with Poorly Controlled Type 2 Diabetes and Acute Myocardial Infarction. *Diabetes & Metabolism*, **45**, 446-452. https://doi.org/10.1016/j.diabet.2019.01.012

[61] Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J., *et al*. (2006) Activation of Oxidative Stress by Acute Glucose Fluctuations Compared with Sustained Chronic Hyperglycemia in Patients with Type 2 Diabetes. *JAMA*, **295**, 1681-1687. https://doi.org/10.1001/jama.295.14.1681

[62] Ceriello, A., Esposito, K., Piconi, L., Ihnat, M.A., Thorpe, J.E., Testa, R., *et al*. (2008) Oscillating Glucose Is More Deleterious to Endothelial Function and Oxidative Stress than Mean Glucose in Normal and Type 2 Diabetic Patients. *Diabetes*, **57**, 1349-1354. https://doi.org/10.2337/db08-0063

[63] Kapellen, T.M., Gausche, R., Dost, A., Wiegand, S., Flechtner-Mors, M., Keller, E., *et al*. (2014) Children and Adolescents with Type 1 Diabetes in Germany Are More Overweight than Healthy Controls: Results Comparing DPV Database and CrescNet Database. *Journal of Pediatric Endocrinology and Metabolism*, **27**, 209-214. https://doi.org/10.1515/jpem-2013-0381

[64] Maffeis, C., Birkebaek, N.H., Konstantinova, M., Schwandt, A., Vazeou, A., Casteels, K., *et al*. (2018) Prevalence of Underweight, Overweight, and Obesity in Children and Adolescents with Type 1 Diabetes: Data from the International SWEET Registry. *Pediatric Diabetes*, **19**, 1211-1220. https://doi.org/10.1111/pedi.12730

[65] Chillarón, J.J., Flores Le-Roux, J.A., Benaiges, D. and Pedro-Botet, J. (2014) Type 1 Diabetes, Metabolic Syndrome and Cardiovascular Risk. *Metabolism*, **63**, 181-187. https://doi.org/10.1016/j.metabol.2013.10.002

[66] Thorn, L.M., Forsblom, C., Wadén, J., Saraheimo, M., Tolonen, N., Hietala, K., *et al*. (2009) Metabolic Syndrome as a Risk Factor for Cardiovascular Disease, Mortality, and Progression of Diabetic Nephropathy in Type 1 Diabetes. *Diabetes Care*, **32**, 950-952. https://doi.org/10.2337/dc08-2022

[67] Reaven, G. (2002) Metabolic Syndrome: Pathophysiology and Implications for Management of Cardiovascular Disease. *Circulation*, **106**, 286-288. https://doi.org/10.1161/01.cir.0000019884.36724.d9

[68] Ganjali, S., Dallinga-Thie, G.M., Simental-Mendía, L.E., Banach, M., Pirro, M. and Sahebkar, A. (2017) HDL Functionality in Type 1 Diabetes. *Atherosclerosis*, **267**, 99-109. https://doi.org/10.1016/j.atherosclerosis.2017.10.018

[69] Vergès, B. (2020) Dyslipidemia in Type 1 Diabetes: A Masked Danger. *Trends in Endocrinology & Metabolism*, **31**, 422-434. https://doi.org/10.1016/j.tem.2020.01.015

[70] Bagdade, J.D., Knight-Gibson, C., Simpson, N., Gerkin, R., Alaupovic, P. and Reardon, C. (2012) CETP-Mediated Cholesteryl Ester Enrichment of APOB Subclasses in Type 1 Diabetes. *European Journal of Clinical Investigation*, **42**, 709-716. https://doi.org/10.1111/j.1365-2362.2011.02636.x

[71] Tsikas, D., Bollenbach, A., Hanff, E. and Kayacelebi, A.A. (2018) Asymmetric Dimethylarginine (ADMA), Symmetric Dimethylarginine (SDMA) and Homoarginine (hArg): The ADMA, SDMA and hArg Paradoxes. *Cardiovascular Diabetology*, **17**, Article No. 1. https://doi.org/10.1186/s12933-017-0656-x

[72] Manjunatha, S., Distelmaier, K., Dasari, S., Carter, R.E., Kudva, Y.C. and Nair, K.S. (2016) Functional and Proteomic Alterations of Plasma High Density Lipoproteins in Type 1 Diabetes Mellitus. *Metabolism*, **65**, 1421-1431. https://doi.org/10.1016/j.metabol.2016.06.008

[73] Perségol, L., Foissac, M., Lagrost, L., Athias, A., Gambert, P., Vergès, B., *et al*. (2007) HDL Particles from Type 1 Diabetic Patients Are Unable to Reverse the Inhibitory Effect of Oxidised LDL on Endothelium-Dependent Vasorelaxation. *Diabetologia*, **50**, 2384-2387. https://doi.org/10.1007/s00125-007-0808-8

[74] Denimal, D., Pais de Barros, J., Petit, J., Bouillet, B., Vergès, B. and Duvillard, L. (2015) Significant Abnormalities of the HDL Phosphosphingolipidome in Type 1 Diabetes Despite Normal HDL Cholesterol Concentration. *Atherosclerosis*, **241**, 752-760. https://doi.org/10.1016/j.atherosclerosis.2015.06.040

[75] Conrad, N., Verbeke, G., Molenberghs, G., Goetschalckx, L., Callender, T., Cambridge, G., *et al*. (2022) Autoimmune Diseases and Cardiovascular Risk: A Population-Based Study on 19 Autoimmune Diseases and 12 Cardiovascular Diseases in 22 Million Individuals in the UK. *The Lancet*, **400**, 733-743. https://doi.org/10.1016/s0140-6736(22)01349-6

[76] Gottumukkala, R.V.S.R.K., Lv, H., Cornivelli, L., Wagers, A.J., Kwong, R.Y., Bronson, R., *et al*. (2012) Myocardial Infarction Triggers Chronic Cardiac Autoimmunity in Type 1 Diabetes. *Science Translational Medicine*, **4**, 138ra180. https://doi.org/10.1126/scitranslmed.3003551

[77] Sousa, G.R., Pober, D., Galderisi, A., Lv, H., Yu, L., Pereira, A.C., *et al*. (2019) Glycemic Control, Cardiac Autoimmunity, and Long-Term Risk of Cardiovascular Disease in Type 1 Diabetes Mellitus. *Circulation*, **139**, 730-743. https://doi.org/10.1161/circulationaha.118.036068

[78] Sousa, G.R., Kosiborod, M., Bluemke, D.A. and Lipes, M.A. (2020) Cardiac Autoimmunity Is Associated with Subclinical Myocardial Dysfunction in Patients with Type 1 Diabetes Mellitus. *Circulation*, **141**, 1107-1109. https://doi.org/10.1161/circulationaha.119.044539

[79] Maack, C., Lehrke, M., Backs, J., Heinzel, F.R., Hulot, J., Marx, N., *et al*. (2018) Heart Failure and Diabetes: Metabolic Alterations and Therapeutic Interventions: A State-of-the-Art Review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *European Heart Journal*, **39**, 4243-4254. https://doi.org/10.1093/eurheartj/ehy596

[80] Kadowaki, T., Maegawa, H., Watada, H., Yabe, D., Node, K., Murohara, T., *et al*. (2022) Interconnection between Cardiovascular, Renal and Metabolic Disorders: A Narrative Review with a Focus on Japan. *Diabetes, Obesity and Metabolism*, **24**, 2283-2296. https://doi.org/10.1111/dom.14829

[81] Dei Cas, A., Khan, S.S., Butler, J., Mentz, R.J., Bonow, R.O., Avogaro, A., *et al*. (2015) Impact of Diabetes on Epidemiology, Treatment, and Outcomes of Patients with Heart Failure. *JACC*: *Heart Failure*, **3**, 136-145. https://doi.org/10.1016/j.jchf.2014.08.004

[82] Li, Y., Liu, B., Li, Y., Jing, X., Deng, S., Yan, Y., *et al*. (2019) Epicardial Fat Tissue in Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Cardiovascular Diabetology*, **18**, Article No. 3. https://doi.org/10.1186/s12933-019-0807-3

[83] Iacobellis, G. (2013) Epicardial Adipose Tissue in Endocrine and Metabolic Diseases. *Endocrine*, **46**, 8-15. https://doi.org/10.1007/s12020-013-0099-4

[84] Iacobellis, G. and Bianco, A.C. (2011) Epicardial Adipose Tissue: Emerging Physiological, Pathophysiological and Clinical Features. *Trends in Endocrinology & Metabolism*, **22**, 450-457. https://doi.org/10.1016/j.tem.2011.07.003

[85] Christensen, R.H., von Scholten, B.J., Lehrskov, L.L., Rossing, P. and Jørgensen, P.G. (2020) Epicardial Adipose Tissue: An Emerging Biomarker of Cardiovascular Complications in Type 2 Diabetes? *Therapeutic Advances in Endocrinology and Metabolism*, **11**. https://doi.org/10.1177/2042018820928824

[86] Fadini, G.P., Boscaro, E., de Kreutzenberg, S., Agostini, C., Seeger, F., Dimmeler, S., *et al*. (2010) Time Course and Mechanisms of Circulating Progenitor Cell Reduction in the Natural History of Type 2 Diabetes. *Diabetes Care*, **33**, 1097-1102. https://doi.org/10.2337/dc09-1999

[87] Fadini, G.P., Albiero, M., Vigili de Kreutzenberg, S., Boscaro, E., Cappellari, R., Marescotti, M., *et al*. (2013) Diabetes Impairs Stem Cell and Proangiogenic Cell Mobilization in Humans. *Diabetes Care*, **36**, 943-949. https://doi.org/10.2337/dc12-1084

[88] Rigato, M., Bittante, C., Albiero, M., Avogaro, A. and Fadini, G.P. (2015) Circulating Progenitor Cell Count Predicts Microvascular Outcomes in Type 2 Diabetic Patients. *The Journal of Clinical Endocrinology & Metabolism*, **100**, 2666-2672. https://doi.org/10.1210/jc.2015-1687

[89] Rigato, M., Avogaro, A. and Fadini, G.P. (2016) Levels of Circulating Progenitor Cells, Cardiovascular Outcomes and Death: A Meta-Analysis of Prospective Observational Studies. *Circulation Research*, **118**, 1930-1939. https://doi.org/10.1161/circresaha.116.308366

[90] Poulsom, R., Forbes, S.J., Hodivala-Dilke, K., Ryan, E., Wyles, S., Navaratnarasah, S., *et al*. (2001) Bone Marrow Contributes to Renal Parenchymal Turnover and Regeneration. *The Journal of Pathology*, **195**, 229-235. https://doi.org/10.1002/path.976

[91] Berezin, A.E., Kremzer, A.A., Samura, T.A., Berezina, T.A. and Martovitskaya, Y.V. (2014) Serum Uric Acid Predicts Declining of Circulating Proangiogenic Mononuclear Progenitor Cells in Chronic Heart Failure Patients. *Journal of Cardiovascular and Thoracic Research*, **6**, 153-162. https://doi.org/10.15171/jcvtr.2014.004

[92] Fadini, G.P. (2013) A Reappraisal of the Role of Circulating (Progenitor) Cells in the Pathobiology of Diabetic Complications. *Diabetologia*, **57**, 4-15. https://doi.org/10.1007/s00125-013-3087-6