Advances in Clinical Medicine 临床医学进展, 2026, 16(7), 1685-1695
Published Online July 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1672691

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达格列净对老年糖尿病前期患者胰岛β细胞功能和内脏脂肪的影响

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收稿日期：2026年6月17日；录用日期：2026年7月11日；发布日期：2026年7月21日

摘 要

目的：探讨达格列净对糖尿病前期患者胰岛β细胞功能和内脏脂肪的影响，并比较对胰岛β细胞功能和内脏脂肪的影响在老年组(≥60岁)与非老年组(<60岁)是否存在差异。方法：选取2024年1月至2024年12月于我院就诊的糖尿病前期患者234例，并根据年龄分为老年组(≥60岁，n = 73)和非老年组(n < 60岁，n = 161)，所有患者均接受达格列净(10 mg，每日一次)联合生活方式干预治疗6个月，收集并比较两组患者治疗前后的临床生化和人体成分分析指标，包括体重、BMI、血糖、胰岛功能、血脂、肝肾功能及内脏脂肪等。结果：(1) 治疗前，两组患者在BMI、收缩压、空腹血糖、糖化血红蛋白、体脂百分比、腰围及内脏脂肪面积等指标上无显著差异(P > 0.05)。老年组舒张压、甘油三酯、总胆固醇、低密度脂蛋白、eGFR、尿酸、空腹胰岛素、HOMA-β及HOMA-IR均显著低于非老年组，而OGTT 2小时血糖显著高于非老年组(P < 0.05)。(2) 干预6个月后，两组空腹血糖、糖化血红蛋白、空腹胰岛素、HOMA-β、HOMA-IR及内脏脂肪面积均较治疗前显著改善(P < 0.05)。其中，老年组空腹血糖由5.32 (5.02, 5.86)降至5.19 (4.78, 5.54) mmol/L，非老年组由5.21 (4.84, 5.69)降至5.11 (4.74, 5.45) mmol/L；糖化血红蛋白老年组由6.00 (5.80, 6.20)降至5.70 (5.50, 5.90)%，非老年组由5.90 (5.60, 6.20)降至5.60 (5.40, 5.90)%；空腹胰岛素老年组由14.57 (11.60, 17.40)降至10.20 (7.72, 11.80) mU/L，非老年组由17.40 (12.20, 26.00)降至13.54 (8.55, 20.40) mU/L。HOMA-β两组均较治疗前显著下降[老年组由155.96 (102.50, 209.91)降至106.83 (87.16, 160.68)，非老年组由212.03 (134.44, 333.33)降至159.41 (103.06, 270.73)，均P < 0.05]；HOMA-IR老年组由3.46 (2.75, 4.22)降至2.24 (1.79, 2.68)，非老年组由4.15 (2.79, 6.05)降至3.04 (1.93, 4.65) (P<0.05)；内脏脂肪面积老年组由81.90 (61.50, 104.70)降至71.70 (44.70, 88.60) cm²，非老年组由84.20 (52.80, 117.60)降至67.60 (41.00, 102.60) cm² (均P < 0.05)。两组在HOMA-β、HOMA-IR、糖化血红蛋白及内脏脂肪面积的变化差值上均无显著差异。两组体脂百分比均显著下降，但老年组降幅低于非老年组(P < 0.05)，老年组由28.50 (21.80, 33.90)降至23.70 (19.90, 26.80)%，非老年组由27.10 (21.50, 35.10)降至19.00 (15.70, 21.50)%。(3) 临床疗效方面，老年组的显效率显著低于非老年组(16.44% vs 29.19%，低12.8%，95%CI：0.7%~24.8%)；老年组有效率亦显著低于非老年组(35.6% vs 54.0%, P < 0.05)。结论：达格列净可显著改善糖尿病前期患者的胰岛功能及胰岛素抵抗，降低内脏脂肪面积，但老年患者达到临床缓解标准的比例明显低于非老年患者。

关键词

达格列净，糖尿病前期，胰岛β细胞功能，内脏脂肪，老年

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文章引用: 何新姣, 张瀚元, 梁韵琦, 祁昱辛, 刘瑞冬, 曹彩霞. 达格列净对老年糖尿病前期患者胰岛β细胞功能和内脏脂肪的影响[J]. 临床医学进展, 2026, 16(7): 1685-1695. DOI: 10.12677/acm.2026.1672691

Effects of Dapagliflozin on the Function of Pancreatic Islet β Cells and Visceral Fat in Elderly Prediabetic Patients

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Received: June 17, 2026; accepted: July 11, 2026; published: July 21, 2026

Abstract

Objective: To investigate the effect of dapagliflozin on islet β cell function and visceral fat in patients with prediabetes, and to compare the effects on islet β cell function and visceral fat in the elderly group (≥60 years old) and the non-elderly group (<60 years old). Methods: A total of 234 patients with prediabetes who attended our hospital from January 2024 to December 2024 were selected and divided into the elderly group (≥60 years, n = 73) and the non-elderly group (n < 60 years, n = 161) according to age. All patients received dapagliflozin (10 mg once daily) combined with lifestyle intervention for 6 months. The clinical biochemical and body composition analysis indexes of the two groups before and after treatment were collected and compared, including body weight, BMI, blood glucose, pancreatic islet function, blood lipids, liver and kidney function, and visceral fat. Results: (1) At baseline, there were no significant differences between the elderly and non-elderly groups in BMI, systolic blood pressure, fasting blood glucose, glycated hemoglobin, body fat percentage, waist circumference, or visceral fat area (all P > 0.05). However, the elderly group exhibited significantly lower levels of diastolic blood pressure, triglycerides, total cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), uric acid, fasting insulin, homeostatic model assessment of β-cell function (HOMA-β), and insulin resistance (HOMA-IR), while their 2-hour oral glucose tolerance test (OGTT) blood glucose was significantly higher than that of the non-elderly group (P < 0.05 for all). (2) After 6 months of intervention, both groups showed significant improvements from baseline in fasting blood glucose, glycated hemoglobin, fasting insulin, HOMA-β, HOMA-IR, and visceral fat area (all P < 0.05). Specifically, fasting blood glucose decreased from 5.32 (5.02, 5.86) to 5.19 (4.78, 5.54) mmol/L in the elderly group, and from 5.21 (4.84, 5.69) to 5.11 (4.74, 5.45) mmol/L in the non-elderly group. Glycated hemoglobin fell from 6.00 (5.80, 6.20) to 5.70 (5.50, 5.90)% in the elderly group and from 5.90 (5.60, 6.20) to 5.60 (5.40, 5.90)% in the non-elderly group. Fasting insulin declined from 14.57 (11.60, 17.40) to 10.20 (7.72, 11.80) mU/L in the elderly group, and from 17.40 (12.20, 26.00) to 13.54 (8.55, 20.40) mU/L in the non-elderly group. HOMA-β decreased significantly in both groups [elderly: from 155.96 (102.50, 209.91) to 106.83 (87.16, 160.68); non-elderly: from 212.03 (134.44, 333.33) to 159.41 (103.06, 270.73); all P < 0.05]. HOMA-IR also decreased significantly [elderly: from 3.46 (2.75, 4.22) to 2.24 (1.79, 2.68); non-elderly: from 4.15 (2.79, 6.05) to 3.04 (1.93, 4.65); P < 0.05]. Visceral fat area reduced from 81.90 (61.50, 104.70) to 71.70 (44.70, 88.60) cm^2 in the elderly group, and from 84.20 (52.80, 117.60) to 67.60 (41.00, 102.60) cm^2 in the non-elderly group (all P < 0.05). No significant between-group differences were observed in the magnitude of change for HOMA-β, HOMA-IR, glycated hemoglobin, or visceral fat area. Body fat percentage decreased markedly in both groups, but the reduction was significantly smaller in the elderly group than in the non-elderly group (P < 0.05): from 28.50 (21.80, 33.90) to 23.70 (19.90, 26.80)% in the elderly, and from 27.10 (21.50, 35.10) to 19.00 (15.70, 21.50)% in the non-elderly. (3) Regarding clinical efficacy, the elderly group had a significantly lower marked response rate compared with the non-elderly group (16.44% vs. 29.19%, difference of 12.8%, 95%CI: 0.7%~24.8%), and the overall effective rate was also significantly reduced in the elderly group (35.6% vs. 54.0%, P < 0.05). Conclusion: Dapagliflozin can

significantly improve pancreatic islet function and insulin resistance and reduce visceral fat area in patients with prediabetes, but the proportion of elderly patients meeting the clinical remission criteria is significantly lower than that of non-elderly patients.

Keywords

Dapagliflozin, Prediabetes, Islet *β* Cell Function, Visceral Fat, Elderly

1. 引言

糖尿病前期是一种血糖水平高于正常，而未达到糖尿病的诊断标准的糖代谢状态，根据空腹血糖、糖耐量试验 2 小时血糖及糖化血红蛋白水平，又分为三种状态，即空腹血糖受损(impaired fasting glucose, IFG)、糖耐量减低(impaired glucose tolerance, IGT)以及两者的混合状态(IFG + IGT) [1]。按照 ADA2010 的诊断标准，我国糖尿病前期的发生率已高达 50.1% [2] [3]，年龄是影响糖尿病前期进展的重要因素。流行病学数据显示，糖尿病前期患者向糖尿病的年转化率可达 5%~10% [4] [5]，相关研究表明老年人患糖尿病前期的风险比年轻人更高，是年轻人的 1.64 倍[3] [6]，糖尿病前期是多种疾病发生的危险因素，包括心脑大血管、微血管、痴呆、肿瘤、感染等[7]-[11]。因此对糖尿病前期人群采取干预措施以降低糖尿病人群的发生率是必要的，处于糖尿病前期的老年人对糖尿病认知较低，通过咨询加强对纠正生活方式的积极态度，可以提高糖尿病前期预防和控制计划的效率，并防止其进展到糖尿病阶段[12]。

研究表明，糖尿病前期患者的发病机制与糖尿病患者相似，均包括胰岛素抵抗及胰岛功能受损[13]-[15]。IFG/IGT 联合导致外周和肝脏胰岛素敏感性的严重缺陷和 *β* 细胞功能的进行性丧失[16]。老年糖尿病患者的胰岛素抵抗和胰岛 *β* 细胞功能与青年人相比存在明显的差异，在糖尿病前期患者中，青年人胰岛素抵抗较老年人更为严重。在空腹血糖受损患者中，年轻组患者的糖尿病发生率明显高于老年组[17]。根据 2023 中国成人糖尿病前期干预的专家共识，糖尿病前期干预的目标是优先通过生活方式干预，控制体重，改善血脂异常等危险因素，最终使得血糖逆转为正常水平[1]。ADA2023 指南建议，对于糖尿病前期人群，可以考虑使用二甲双胍预防糖尿病[18]-[20]。阿卡波糖是目前唯一在我国获得 IGT 适应症的药物。有研究报道，钠－葡萄糖协同转运蛋白 2 (sodium-dependent glucose transporters 2, SGLT-2)抑制剂恩格列净能够逆转糖尿病前期患者胰岛素抵抗，改善胰岛功能，并且能够改善肥胖及全身代谢情况[21]。SGLT-2 抑制剂达格列净能够改善 2 型糖尿病患者的胰岛素抵抗[22]。

目前关于 SGLT-2 抑制剂对糖尿病前期患者胰岛功能及内脏脂肪的影响的研究较少。尤其在老年糖尿病前期中的作用尚未见报道。本研究旨在：评价达格列净对糖尿病前期患者胰岛 *β* 细胞功能和内脏脂肪的影响，并比较不同年龄分组中的差异。

2. 研究对象及方法

2.1. 资料与方法

2.1.1. 一般资料

选择 2024.01~2024.12 年在我院治疗的糖尿病前期患者 234 例为研究对象。纳入标准：(1) 符合糖尿病前期诊断标准[1] [23] [24]：在 75 g 口服葡萄糖耐量试验期间，IFG：6.1 mmol/L ≤ 空腹血糖 < 7.0 mmol/L，OGTT 2 h 血糖 < 7.8 mmol/L；IGT：空腹血糖 < 7.0 mmol/L 且 7.8 mmol/L ≤ OGTT 2 h 血糖 < 11.1 mmol/L；

HbA1c：5.7%~6.4%；(2) 年龄大于 18 周岁；(3) 近 3 个月内均未接受任何促胰岛素分泌剂及长效胰岛素治疗；(4) 近 3 个月未使用过糖皮质激素、特殊营养品等影响糖代谢的药物；(5) 受检前 12 h 停用任何控制血糖及血脂的药物，受检前 1 周内无急性上呼吸道感染等感染性疾病；(6) 经医院伦理委员会批准，所有患者依从性良好，均对本研究知情并签署知情同意书，排除标准：(1) 2 型糖尿病及其他类型糖尿病；(2) 妊娠及哺乳期患者；(3) 药物过敏者；(4) 智力低下及患有精神疾病不能配合者。(5) 肾功能受损，定义为筛选期间确定的 eGFR < 60 mL/min。(6) 易患泌尿生殖系统感染。(7) 已知自身免疫性疾病(甲状腺自身免疫性疾病除外)。(8) 使用导致体重显著增加或减轻的药物；(9) 胰腺炎病史、重度抑郁、多发性内分泌瘤 2 型或家族性甲状腺髓样癌家族史或个人史；(10) 合并重度心脏瓣膜疾病、恶性肿瘤；重度脏器受损合并急、慢性感染；(11) 筛选前 12 个月内发生任何相关(根据研究者判断)心血管疾病，例如心肌梗死、急性冠脉综合征。(12) 肝病指征。

2.1.2. 方法

两组患者均给予糖尿病前期健康教育、饮食控制、适量运动。老年组及非老年组均给予口服达格列净片(阿斯利康制药有限公司，国药准字 J20170040，规格：10 mg × 14 片/盒)。每日 1 次，每次 1 片。连续治疗 6 月，分别在治疗前、治疗后给予患者抽取静脉血检查，所有受试者检查前均禁食 10 小时，至次日 7:00~9:00 空腹抽取肘中静脉血进行相关检测。

2.2. 观察指标及评价标准

2.2.1. 一般资料采集

收集患者年龄、性别、血压、体重指数等基本信息。

2.2.2. 血糖代谢指标

所有受试者于试验前 3 天维持正常碳水化合物摄入(每日不低于 150 g)，禁食 10~14 小时后，于次晨 7:00~9:00 进行检测。先抽取空腹静脉血测定空腹血糖(FPG)，随后将 75 g 无水葡萄糖溶于 300 ml 温水中，嘱受试者于 5 分钟内饮完。从饮第一口糖水开始计时，于服糖后 60 分钟、120 分钟分别抽取静脉血，采用己糖激酶法测定血浆葡萄糖浓度及胰岛素浓度。整个试验期间受试者保持安静、禁食、禁烟、避免剧烈活动。收集以下指标：(1) 空腹血糖(GLU)；(2) 餐后 2 h 血糖(GLU120)；(3) 糖化血红蛋白(HbA1c)；(4) 空腹胰岛素(FINS)；(5) 120 分钟胰岛素(2-hFINS)。

2.3. 胰岛 β 细胞功能评估

采用稳态模型评估以下指标：

- $\text{HOMA-}\beta = 20 \times \text{FINS}(\text{mU/L}) / [\text{GLU}(\text{mmol/L}) - 3.5]$
- $\text{HOMA-IR} = \text{GLU}(\text{mmol/L}) \times \text{FINS}(\text{mU/L}) / 22.5$

2.4. 血脂及其他指标

所有受试者于治疗前及治疗 6 个月后，禁食 8~10 小时，于次日清晨 7:00~9:00 采集空腹肘静脉血 5 ml，分别置于真空促凝管中。血液标本采集后常温静置 30 分钟，以 3000 r/min 离心 10 分钟，分离血清/血浆后于 2 小时内完成检测。各项指标检测严格按照仪器及试剂盒说明书操作。收集血脂、肾小球滤过率、钾离子、钠离子、尿酸等资料。

2.5. 内脏脂肪等人体成分评估

采用生物电阻抗分析法(InBody 770，韩国 Biospace 公司)测量以下身体成分指标：(1) 体重(kg)；(2)

腰围(cm)；(3) 体脂百分比(%)；(4) 内脏脂肪面积(cm^2)；(5) 骨骼肌指数(SMI)，内脏脂肪面积(VFA)由设备自动计算。

2.6. 判断糖尿病前期是否逆转的标准

本研究根据国际通用标准，2025 美国糖尿病协会 ADA 标准：主要依据以下三个指标：(1) 空腹血糖 < 5.6 mmol/L；(2) 口服葡萄糖耐量试验 2 小时血糖 < 7.8 mmol/L；(3) 糖化血红蛋白 < 5.7%；(4) 逆转同时需要满足持续性稳定：至少两次检测(间隔 3~6 个月)达标。(5) 即使未完全逆转，HbA1c 降低 0.3%即可显著减少糖尿病发生风险。减重 5%可使胰岛素敏感性提高 50%以上。

2.7. 统计学处理

所得数据采用 SPSS 27.0 软件进行统计分析。正态分布计量资料以均数 ± 标准差($\bar{x} \pm s$)表示，组内治疗前后比较采用配对 t 检验，组间比较采用独立样本 t 检验；非正态分布资料以中位数(四分位数间距)表示，采用 Wilcoxon 秩和检验。计数资料以例数(%)表示，组间比较采用 χ^2 检验或 Fisher 精确概率法。以 $P < 0.05$ 为差异有统计学意义。

3. 结果分析

3.1. 两组患者基线一般资料比较

本研究共纳入 234 例糖尿病前期患者，其中老年组 73 例(33.2%)，非老年组 161 例(68.8%)。两组患者基线资料比较见表 1。

Table 1. Comparison of general baseline data between the two groups
表 1. 两组患者基线一般资料比较

	老年组(n = 73)		非老年组(n = 161)		P 值
	治疗前	治疗后	治疗前	治疗后	
BMI (Kg/m^2)	26.45 (24.61, 28.91)	25.50 (24.00, 27.40)**	26.69 (23.34, 29.76)	25.60 (24.20, 27.80)**	0.451
SBP (mmHg)	150 (137, 170)	136 (133, 142)**	150 (136, 169)	136 (133, 141)**	0.085
DBP (mmHg)	75 (64, 85)	76 (65, 86)	91 (84, 102)	86 (80, 96)*	<0.001*
TG (mmol/L)	1.32 (0.87, 2.01)	1.31 (0.78, 1.79)	1.74 (1.17, 2.46)	1.21 (0.85, 1.77)**	<0.001*
TC (mmol/L)	4.57 (3.77, 5.21)	4.59 (3.91, 5.17)	5.15 (4.39, 5.79)	5.03 (4.41, 5.74)	<0.001*
HDL (mmol/L)	1.38 (1.22, 1.65)	1.43 (1.26, 1.60)	1.49 (1.26, 1.60)	1.44 (1.23, 1.69)	0.158
LDL (mmol/L)	2.52 (2.05, 3.10)	2.62 (2.18, 3.11)	2.88 (2.42, 3.55)	2.91 (2.39, 3.47)	0.003*
eGFR	71.68 (64.63, 85.61)	81.39 (70.35, 87.81)	78.59 (68.34, 90.50)	83.71 (74.24, 91.41)*	0.025*
UA (mmol/L)	362.0 (308.0, 396.0)	324.0 (270.0, 377.2)*	377.7 (326.0, 446.0)	354.1 (294.0, 416.0)*	0.034*

注：BMI：体重指数；SBP：收缩压；DBP：舒张压；TG：甘油三酯；TC：总胆固醇；HDL：高密度脂蛋白；LDL：低密度脂蛋白；eGFR：肾小球滤过率；UA：尿酸；与同组治疗前比较，**P < 0.001，*P < 0.05；与非老年组治疗前比较，*P < 0.05。

结果显示：(1) 两组患者治疗前在 BMI、收缩压上无显著差异(P > 0.05)；老年组舒张压、甘油三酯、总胆固醇、低密度脂蛋白、eGFR、尿酸均显著低于非老年组(P < 0.05)。(2) 干预 6 个月后，两组患者 BMI、

SBP、尿酸均较前改善(P < 0.05)，而舒张压、甘油三酯、肾小球滤过率等指标在非老年组中较前也显著改善(P < 0.05)。

3.2. 两组患者治疗前后血糖代谢指标比较

治疗 6 月后，两组空腹血糖、餐后 2 h 血糖、糖化血红蛋白及空腹胰岛素均较治疗前显著下降(P < 0.05)。治疗后两组 HOMA-β 均较治疗前显著下降(P 均<0.05)，两组 HOMA-IR 均显著改善(P < 0.05)，见表 2。

Table 2. Comparison of blood glucose metabolism indicators before and after treatment in the elderly and non-elderly groups
表 2. 老年组和非老年组治疗前后血糖代谢指标比较

	老年组(n = 73)		非老年组(n = 161)		P 值
	治疗前	治疗后	治疗前	治疗后	
FPG (mmol/L)	5.32 (5.02, 5.86)	5.19 (4.78, 5.54)*	5.21 (4.84, 5.69)	5.11 (4.74, 5.45)*	0.052
2-hPG (mmol/L)	9.40 (8.43, 10.25)	8.42 (6.82, 9.58)*	8.59 (7.66, 9.80)	7.50 (6.53, 8.53)**	0.004*
FINS (mU/L)	14.57 (11.60, 17.40)	10.20 (7.72, 11.8)**	17.40 (12.20, 26.00)	13.54 (8.55, 20.40)*	<0.001*
2-hINS (mU/L)	130.00 (79.30, 182.48)	152.30 (116.10, 172.30)	126.14 (78.3, 189.00)	153.20 (131.00, 166.10)	0.991
HbA1c (%)	6.00 (5.80, 6.20)	5.70 (5.50, 5.90)**	5.90 (5.60, 6.20)	5.60 (5.40, 5.90)**	0.285
HOMA-β	155.96 (102.50, 209.91)	106.83 (87.16, 160.68)**	212.03 (134.44, 333.33)	159.41 (103.06, 270.73)*	<0.001*
HOMA-IR	3.46 (2.75, 4.22)	2.24 (1.79, 2.68)**	4.15 (2.79, 6.05)	3.04 (1.93, 4.65)**	0.003*

注：FPG：空腹血糖；2-hPG：OGTT 2 小时葡萄糖；FINS：空腹胰岛素；2-hINS：OGTT 2 小时胰岛素；HbA1c：糖化血红蛋白；HOMA-β：β 细胞功能稳态模型评估指数；HOMA-IR：胰岛素抵抗指数；与同组治疗前比较，**P < 0.001，*P < 0.05，与非老年组治疗前比较，*P < 0.05。

3.3. 两组患者治疗前后内脏脂肪等人体成分比较

两组治疗后体脂百分比、内脏脂肪面积均显著下降(P 均<0.05)，腰围及骨骼肌指数较治疗前无显著改善(P > 0.05)，见表 3。

Table 3. Comparison of visceral fat and body composition before and after treatment in elderly and non-elderly patients
表 3. 老年组和非老年组患者治疗前后内脏脂肪及人体成分比较

	老年组(n = 73)		非老年组(n = 161)		P 值
	治疗前	治疗后	治疗前	治疗后	
PBF	28.50 (21.80, 33.90)	23.70 (19.90, 26.80)**	27.10 (21.50, 35.10)	19.00 (15.70, 21.50)**	0.858
Wais	84.30 (75.90, 91.40)	81.90 (75.10, 90.70)	83.80 (74.90, 95.20)	82.60 (75.60, 93.40)	0.831
VFA	81.90 (61.50, 104.70)	71.70 (44.70, 88.60)**	84.20 (52.80, 117.60)	67.60 (41.00, 102.60)**	0.850
SMI	7.90 (7.30, 8.65)	8.30 (7.50, 9.05)	8.40 (7.60, 9.10)	8.20 (7.40, 9.30)	0.022*

注：PBF：体脂百分比；Wais：腰围；VFA：内脏脂肪面积；SMI：骨骼肌指数；与同组治疗前比较，**P < 0.001，*P < 0.05，与非老年组治疗前比较，*P < 0.05。

3.4. 两组患者治疗前后关键指标变化的比较

结果发现两组体脂百分比均显著下降，但老年组降幅低于非老年组($P < 0.05$)，胰岛β细胞功能指数、胰岛素抵抗指数、糖化血红蛋白、内脏脂肪面积变化无显著差异($P > 0.05$)，见表 4。

Table 4. Comparison of changes in key indicators before and after treatment in the two groups of patients
表 4. 两组患者治疗前后关键指标变化的比较

	老年组(n = 73)	非老年组(n = 161)	P 值
HOMA-β	−31.69 (−97.08, 15.03)	−19.61 (−139.59, 66.26)	0.489
HOMA-IR	−1.00 (−1.91, −0.2)	−1.01 (−2.44, 0.28)	0.467
HbA1c (%)	−0.3 (−0.6, 0.10)	−0.3 (−0.6, 0.00)	0.788
PBF (%)	−5.10 (−7.70, −2.00)	−9.20 (−14.00, −5.00)	<0.001*
VFA (cm²)	−11.10 (−20.10, −7.50)	−9.00 (−17.00, −7.10)	0.448

注：HOMA-β：β细胞功能稳态模型评估指数；HOMA-IR：胰岛素抵抗指数；HbA1c：糖化血红蛋白；PBF：体脂百分比；VFA：内脏脂肪面积；与非老年组治疗前比较，*$P < 0.05$。

3.5. 两组患者临床疗效比较

符合糖尿病前期缓解标准前两项条件的代表有效，达到缓解标准代表显效。老年组的显效率比非老年组低 12.8% (95%CI: 0.7%~24.8%)，有效率比非老年组低 18.4% ($P < 0.05$)，差异有统计学意义，见表 5。

Table 5. Comparison of clinical efficacy between the two groups of patients
表 5. 两组患者临床疗效比较

	显效(%)	有效(%)
非老年组(n = 161)	47 (29.19)	87 (54.0)
老年组(n = 73)	12 (16.44)	26 (35.6)*

注：与非老年组比较，*$P < 0.05$。

4. 讨论

糖尿病和糖尿病前期与预期寿命缩短和全因死亡风险增加显著相关[25]。本研究基线数据显示，老年组与非老年组在 BMI、收缩压、糖化血红蛋白等指标上无显著差异，但在舒张压、HOMA-β、HOMA-IR、空腹胰岛素、低密度脂蛋白、肾小球滤过率、尿酸水平上存在明显差异。老年组 HOMA-β 显著低于非老年组，HOMA-IR 也显著低于非老年组。这一结果揭示了老年糖尿病前期人群独特的代谢特征：以β细胞功能储备不足为主要矛盾，而非老年组则以胰岛素抵抗更为突出，这与上述研究结果一致。动物实验和人体研究均证实，随年龄增长，β细胞的增殖能力显著下降，端粒缩短、线粒体功能障碍、自噬受损等机制共同导致β细胞数量减少和功能衰退[26]。

目前尚无指南指出将 SGLT 2 抑制剂应用于糖尿病前期的患者，多种研究表明，达格列净通过多种机制诱导β细胞再生，改善β细胞功能及胰岛细胞的敏感度[27]-[31]。最新一项研究表明，达格列净可以通过上调 GLP-1 的产生来促进胰腺β细胞的再生，而 GLP-1 的产生是通过肠道菌群和色氨酸代谢来介导的，该研究向我们揭示了肠道菌群－色氨酸代谢-GLP-1 轴是达格列净诱导β细胞再生的新的机制，为我

们对糖尿病及糖尿病前期的治疗提供了有力的试验证据[32]。Virginia Reverte 等人研究表明达格列净与 sGC 刺激剂联合用药能够更有效降低高脂饮食的高血压大鼠的血压，更是同步改善了大鼠的葡萄糖耐量，显著抑制了大鼠体重的增加，降低了胰岛素抵抗指数与肾血管阻力，并且减轻了大鼠肾脏细胞的炎细胞浸润，这比任一单药治疗效果更佳，提示达格列净能够增强 sGC 刺激剂对长期高脂饮食所致的心肾代谢多重损伤的逆转作用[33]。

达格列净改善胰岛素抵抗的机制已在多项研究中得到证实。达格列净通过促进尿糖排泄造成热量负平衡[34]。这种热量丢失促进体内脂肪分解供能，从而改善胰岛素敏感性。此外，SGLT2 抑制剂还可通过减轻脂毒性、降低炎症因子水平等机制改善胰岛素抵抗[35]。Veelen 等人在糖尿病前期胰岛素抵抗个体中的随机双盲交叉试验也证实，达格列净治疗 14 天即可显著提高 24 小时脂肪氧化率和骨骼肌线粒体氧化能力，这些代谢适应性的改变有助于改善胰岛素抵抗[34]。本研究发现，治疗 6 月后，两组空腹血糖、餐后 2h 血糖、糖化血红蛋白及空腹胰岛素均较治疗前显著下降($P < 0.05$)。同时，两组 HOMA-IR 均显著改善。有研究表明恩格列净通过增强脂肪利用抑制体重增加，并且减轻肥胖诱导的炎症和胰岛素抵抗[36]，这能够充分支持我们的研究结果。本研究中，治疗后两组 HOMA-β 均较治疗前显著下降。HOMA-β 的下降可能反映了达格列净治疗后 β 细胞负荷的真实变化，而非 β 细胞功能的进一步恶化。这实际上反映了 β 细胞从“高负荷代偿状态”向“低负荷休整状态”的转变。

从机制角度分析，达格列净对 β 细胞功能的影响是多层面的。首先，达格列净通过降低血糖，直接解除高血糖对 β 细胞的“糖毒性”作用。长期高血糖可通过氧化应激、内质网应激等途径诱导 β 细胞凋亡和功能障碍[26]。其次，达格列净可减轻脂毒性对 β 细胞的损伤。本研究中两组内脏脂肪面积的显著下降证实了这一点。内脏脂肪减少后，循环游离脂肪酸水平下降，减轻了对 β 细胞的脂毒性损伤[37]。Bolinder 等人在动物模型中的研究也表明，SGLT2 基因敲除可改善葡萄糖稳态并保护胰岛 β 细胞功能[38]。因此，本研究观察到的 HOMA-β 下降应被解读为 β 细胞代谢负荷降低的标志。相关研究显示内脏脂肪面积可以增加胰岛素抵抗[37]-[39]，达格列净可以改善内脏脂肪面积、体脂百分比[40] [41]，在本研究中，老年组及非老年组糖尿病前期患者使用达格列净治疗后，患者内脏脂肪面积及体脂肪百分比获得较为明显改善。内脏脂肪分泌游离脂肪酸、肿瘤坏死因子-α、白细胞介素-6 等多种炎症因子，不仅直接诱导外周胰岛素抵抗，还可通过脂毒性途径诱导 β 细胞凋亡。Bolinder 等人的研究显示，达格列净治疗可显著减少 2 型糖尿病患者的总体脂和内脏脂肪组织分布。张秀娟等[28]的研究也证实，达格列净可显著降低老年肥胖型 2 型糖尿病患者的腰臀比、BMI 及内脏脂肪指数。

本研究中，患者经达格列净治疗后，血脂水平也明显得到了改善，这一结果与其他研究结果也相吻合。一项单中心、随机、前瞻性研究纳入了 80 例服用处方口服降糖药的 2 型糖尿病患者。患者被分配接受达格列净($n = 40$)或西格列汀($n = 40$)作为辅助治疗。结果显示达格列净和西格列汀可降低 HbA 1c (分别为 0.75%和 0.63%) [42]。此外，多项研究表明达格列净显著降低体重、收缩压、血浆甘油三酯和肝转氨酶[43]-[45]。本研究发现，非老年组治疗后甘油三酯显著下降，而老年组甘油三酯无明显变化。两组 HDL、LDL、总胆固醇治疗前后均无明显变化。在肾功能方面，非老年组治疗后 eGFR 较治疗前显著升高，老年组 eGFR 有上升趋势但未达统计学意义。在本研究中，达格列净治疗后，患者的尿酸水平显著低于治疗前基线水平。这与其他研究是一致的，Danii L S Suijk 等人研究表明了 SGLT 2 抑制剂诱导尿酸排泄，这与尿糖排泄密切相关[46]。

本研究存在以下局限性。首先是缺乏平行的空白对照组，这使得我们无法准确剥离出研究药物的净效应，其次，本研究为单中心、非随机化设计，所有受试者均来自同一临床机构，且分组并非通过随机化实现，这限制了研究结果向更广泛人群或不同医疗场景的外推性，也增大了选择偏倚和分配混杂因素的影响，未来需要我们在多中心、随机对照实验中进一步验证。

5. 结论

综上所述，在糖尿病前期患者中，为期 6 个月的达格列净联合生活方式干预，可显著改善糖尿病前期患者的胰岛功能及胰岛素抵抗，降低内脏脂肪面积，然而，与非老年患者相比，老年糖尿病前期患者的临床缓解率更低，提示我们应早期诊断糖尿病前期，及时干预，从而预防和延缓进展为 2 型糖尿病。

声　明

本研究获得青岛大学附属医院伦理委员会批准(审批号：QYFYWZLL29905)。

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