

二甲双胍治疗2型糖尿病的不良反应及联合用药的应用

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摘要:二甲双胍是目前临床上应用最广泛的降糖药物之一,被多数指南推荐为基础初始用药,但单药治疗时仍可能无法有效控制血糖,已有将二甲双胍与其他类型口服降糖药的联合应用治疗2型糖尿病,包括磺脲类、格列奈类、噻唑烷二酮类、 α -葡萄糖苷酶抑制剂、二肽基酶4抑制剂以及钠-葡萄糖协同转运蛋白2抑制剂等,有效地控制血糖、改善胰岛素抵抗、控制体重、干预肥胖、减轻不良反应,帮助控制血压、降低心血管疾病风险,对改善患者预后有明显作用。本文现对二甲双胍治疗的不良反应及其作为基础的口服降糖药物联合其他药物治疗治疗2型糖尿病的应用进行综述,以期临床2型糖尿病的治疗提供参考。

关键词:2型糖尿病;口服降糖药;二甲双胍;联合用药

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Adverse Reactions of Metformin in the Treatment of Type 2 Diabetes and the Application of Combined Medication

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Abstract: Metformin is currently one of the most widely used hypoglycemic drugs in clinical practice. It is recommended by most guidelines as the basic initial medication. However, it may not be able to effectively control blood sugar during single-agent therapy. Metformin has been used in combination with other types of oral hypoglycemic drugs. Treatment of type 2 diabetes, including sulfonylureas, glinides, thiazolidinediones, α -glucosidase inhibitors, dipeptidylase 4 inhibitors and sodium-glucose cotransporter 2 inhibitors, etc., effectively control blood sugar, improve insulin resistance, control weight, interfere with obesity, reduce adverse reactions, help control blood pressure, reduce the risk of cardiovascular disease, and have a significant effect on improving the prognosis of patients. This article reviews the adverse effects of metformin treatment and the application of the basic oral hypoglycemic drugs combined with other drugs in the treatment of type 2 diabetes, in order to provide a reference for the clinical treatment of type 2 diabetes.

Key words: Type 2 diabetes; Oral hypoglycemic drugs; Metformin; Combination medication

随着人们物质生活水平的提高,2型糖尿病(type 2 diabetes mellitus, T2DM)的发病趋势逐渐呈现年轻化、低龄化的趋势。最新流行病学数据表明,我国目前糖尿病患者总人数估计超过1.2亿人^[1],已成为世界上糖尿病患者最多的国家,且糖尿病的患病率仍逐年上升,尤其是2型糖尿病,占95%以上^[2,3]。2型糖尿病患者如长期血糖控制不佳,可引起多种严重并发症,如肾功能损害^[4]、神经病变^[5]、心血管损害^[6]等,严重降低患者的生存质量。目前,口服降糖药物仍是2型糖尿病患者控制血糖的主要方式,主要包括双胍类、磺脲类、格列奈类等。其中,二甲双胍被大多数临床指南推荐为基础初始用药,临床上也常围绕二甲双胍进行联合用药,本文综述了二甲双胍与其他类型口服药物联合治疗2型糖尿病的临床应用研究,以期今后2型糖尿病的治疗提供参考。

1 二甲双胍治疗2型糖尿病的机制

二甲双胍作为双胍类的代表药物,是目前临床上应用最广泛的降糖药物之一,其作用机制为加速外周组织摄取和利用葡萄糖,减少脂肪分解,增加甘油三酯摄取,抑制肝脏糖异生^[7-9]。临床研究证实无论是单药还是联合治疗,二甲双胍均能有效降低糖

化血红蛋白水平,利于控制2型糖尿病病情。同时,二甲双胍对于2型糖尿病危险因素的作用也被广泛研究。研究表明^[10,11],肥胖是2型糖尿病的重要危险因素之一。控制体重或改善肥胖以预防或治疗2型糖尿病一直是相关研究热点。Apolzan JW等^[12]的研究表明,长期服用二甲双胍可以减轻体重,可能对预防糖尿病的发生有一定作用。Worsley R等^[13]发现二甲双胍可改善2型糖尿病患者的胰岛素抵抗。此外,心血管疾病(cardiovascular disease, CVDs)也是2型糖尿病的危险因素,而2型糖尿病患者出现的糖脂代谢紊乱也增加CVDs风险^[14]。Paul SK等^[15]在研究中观察到二甲双胍降低了2型糖尿病患者CVDs风险;而Indhavivadhana S等^[16]在一项随机对照试验中发现二甲双胍不能明显降低患者的心血管危险因素,因此,可能需要更多的研究以证实二甲双胍在改善2型糖尿病患者心血管事件风险中的作用。

2 不良反应

2.1 胃肠道反应 二甲双胍常见的胃肠道反应主要包括恶心、呕吐、消化不良、腹胀、腹泻^[17]等。而近年来二甲双胍剂型的改变,如二甲双胍肠溶片的出现极大地降低了这些胃肠道不良反应。也有研究发现添加胃肠微生物调节剂可中和二甲双胍所导致的胃肠道反应^[18]。因此,二甲双胍剂型对其不良反应的改善在未来值得进一步研究。

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2.2 低血糖 口服降糖药物以及使用胰岛素在应用过程中都可能出现低血糖,轻者无症状,重者出现低血糖昏迷,但是其发生率难以确定。**Lamounier RN**等^[19]的研究发现,超过半数的2型糖尿病患者至少发生一次低血糖事件,其中,无症状低血糖约占10.6%,而严重低血糖事件约占10.3%。二甲双胍通常不引起低血糖事件,但仍可发生于少数特异患者,如合并代偿性高胰岛素血症的患者可能存在胰岛素分泌延迟,使用二甲双胍降糖后机体分泌的胰岛素并未即时减少,从而引起低血糖事件。2型糖尿病患者发生严重低血糖事件时可危及生命,因此在用药过程中必须密切监测血糖,积极预防低血糖发生。

2.3 乳酸中毒 二甲双胍可诱导细胞从有氧代谢转变为无氧代谢,改变了乳酸循环,被认为是其引起乳酸堆积、乳酸中毒的机制^[20]。而乳酸中毒是二甲双胍的严重不良反应之一,其主要表现为头晕、嗜睡、呼吸困难等。二甲双胍引起乳酸中毒的发病率极低^[21],但死亡率却高达50%^[22]。因此,在用药过程中需避免一次性使用大量药物,避免乳酸中毒发生^[23]。

2.4 维生素B₁₂缺乏 二甲双胍引起2型糖尿病患者维生素B₁₂缺乏的发生率约为7%~22.5%^[24-26]。既往研究显示,二甲双胍致维生素B₁₂缺乏可引起2型糖尿病患者出现巨幼红细胞贫血^[27]。二甲双胍引起2型糖尿病患者维生素B₁₂缺乏的机制目前尚未完全清楚。

2.5 其他 除上述不良反应外,二甲双胍还可导致肝脏损害^[28]、诱发急性胰腺炎^[29]、导致低镁血症^[30]以及引起白细胞破裂性血管炎^[31]等。这些不良反应的发生率较低,在用药时把握好药物适应症与禁忌证并控制好药物用量可避免发生。

3 联合用药

尽管二甲双胍作为治疗2型糖尿病的基础初始用药被广泛应用,但临床上仍然存在许多2型糖尿病患者无法通过二甲双胍单药治疗达到有效的血糖控制,需考虑联合其他口服降糖药物以达到理想的血糖水平。2020美国糖尿病协会(american diabetes association, ADA)糖尿病医学诊疗标准中推荐对于糖化血红蛋白A1C水平高于控制目标1.5%~2.0%的患者,当尽早考虑开始联合用药方案;而对于单用二甲双胍治疗3个月后仍未达到糖化血红蛋白控制目标的患者,应考虑与包括胰岛素等不同类型的降糖药物进行联合^[32]。联合用药有助于提升血糖的控制效率,并有益于糖尿病的一些常见并发症和合并症的治疗。因此,临床上需要根据患者的实际情况选择合适的治疗方案,以达到最佳的治疗效果,提高患者的生存质量。

3.1 联合磺脲类药物 磺脲类降糖药主要的作用机

制是刺激胰岛β细胞释放胰岛素,增强胰岛素敏感性并改善胰岛素抵抗^[33]。研究显示^[34],二代磺脲类药物的代表药物格列吡嗪较其他降糖药物更容易出现低血糖事件。二甲双胍与格列吡嗪联用可取长补短,增强降糖效果并减轻医疗负担。但是两药联用可能会增加CVDs的风险,还需要更多研究来进一步证实^[35]。作为第三代磺脲类药物的代表,格列美脲不仅具有促胰岛素分泌的胰内作用,还可发挥促进外周组织对葡萄糖摄取的胰外降糖作用^[36,37]。**Kokic S**等^[38]研究发现,二甲双胍和格列美脲联合应用可以明显降低患者的餐后血糖水平。**González-Ortiz M**等^[39]的研究发现,二甲双胍与格列美脲联合应用时,低血糖事件的发生更少;此外,**Kabadi UM**等^[40]研究显示,两药联用的效果在实现血糖控制目标的方面甚至优于注射胰岛素,这有益于那些只愿意使用口服药物的患者。因此,在临床上将两药联合应用时能使患者得到更安全的治疗和更好的满意度。

3.2 联合格列奈类药物 与磺脲类药物相比,格列奈类代表药物瑞格列奈起效更快,起效更快,作用时间更短。**Kawamori R**等^[41]的研究证实二甲双胍联合瑞格列奈治疗2型糖尿病有较好的疗效及安全性。研究显示,^[42]两药联用不会增加患者低血糖的风险。目前,临床上已有二甲双胍和瑞格列奈的复方制剂在使用,还有研究者开发出了控释片剂^[43],使其药效更加稳定。

3.3 联合噻唑烷二酮类药物 噻唑烷二酮类药物属于胰岛素增敏剂,其机制是通过激动过氧化物酶体增殖活化受体激动剂,增强胰岛素信号传导,从而提升外周组织对胰岛素的敏感性^[44]。罗格列酮是常用的一种噻唑烷二酮类药物,其与二甲双胍联用可以很好地发挥互补作用,并降低2型糖尿病患者代谢紊乱。**Nie JM**等^[45]的研究发现,两药联用能提升血清脂联素(另一种胰岛素增敏激素)水平,有利于抗肥胖及抗血管粥样硬化^[46];**Li Y**等^[47]研究发现,二甲双胍联合罗格列酮能明显降低患者的总胆固醇和甘油三酯水平,有益于合并有血脂异常的患者。吡格列酮作用机制与罗格列酮相近,但既往研究提示吡格列酮会让患者的体重和体质指数增加^[48],而二甲双胍的减轻体重、抗肥胖作用可部分抵消吡格列酮的副作用。研究显示,二甲双胍联合吡格列酮不仅可以改善2型糖尿病患者的胰岛素抵抗^[49],还可用于改善多囊卵巢综合症患者的胰岛素抵抗^[50]。此外,**Lu CH**等^[51]发现,两药联用有助于降低2型糖尿病患者患痴呆症的风险,提示此方案可能更适合老年患者。

3.4 联合α-葡萄糖苷酶抑制剂 α-葡萄糖苷酶抑制剂通过在小肠内与糖类竞争水解糖类的酶,延缓或减少糖类吸收,从而发挥降糖作用^[52],临床常用的该

类药物有阿卡波糖、米格列醇等。尽管二甲双胍和阿卡波糖联用时的肠道副作用较单独用药风险更高,但研究表明二者联用可有效控制血糖及糖化血红蛋白水平并降低低血糖事件^[53]。Derosa G 等^[54]的研究表明,在二甲双胍的基础治疗方案上添加阿卡波糖后可有效降低患者的餐后血糖水平。因此,对于临床上以餐后血糖升高为主要特点的患者可以优先考虑此方案。米格列醇为较新型的糖苷酶抑制剂,其引发的胃肠道反应较阿卡波糖较少。早期的研究就已证实两药联合应用的安全性及有效性^[55],且在两药联用的基础上加用新型的二肽基肽酶 4 抑制剂类药物能使患者更好地控制血糖和抵抗肥胖。此外,二甲双胍联合米格列醇方案在 2 型糖尿病患者的 CVDs 保护作用值得进一步研究。

3.5 联合二肽基肽酶 4 抑制剂 二肽基肽酶 4 抑制剂(dipeptidyl peptidase 4 inhibitors, DPP-4Is)的主要作用是抑制胰高血糖素样肽 1 (glucagon-like peptide-1, GLP-1)的降解、失活,并维持其活性,而 GLP-1 的作用即为促进胰岛素分泌,抑制糖原分解,从而达到降低血糖的目的^[56]。DPP-4 抑制剂的代表药物有沙格列汀、西格列汀等。Dou J 等^[57]的研究证实,二甲双胍联合沙格列汀治疗 2 型糖尿病在血糖控制效果和低血糖发生率等方面优于两药分别单独应用。此外,有越来越多的研究将达格列净加入到治疗方案中进行三联治疗,使更多的患者达到了血糖控制目标^[58]。而 Yan J 等^[59]比较了二甲双胍分别联合西格列汀、利拉鲁肽、甘精胰岛素的治疗效果发现,二甲双胍联合西格列汀或利拉鲁肽都取得了较好的血糖控制效果,而且能降低体重和肝内脂质,说明该方案比较适合合并有非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)的患者。

3.6 联合钠-葡萄糖协同转运蛋白 2 抑制剂 钠-葡萄糖协同转运蛋白 2(sodium-glucose co-transporter 2, SGLT-2)抑制剂通过抑制葡萄糖在肾脏的重吸收从而达到降低血糖的目的,存在葡萄糖在泌尿系统局部浓度过高的副作用。既往研究显示^[60],SGLT-2 抑制剂的使用可能增加泌尿生殖系统感染风险,而 2 型糖尿病患者本身就是易发生感染的高风险人群,所以在选用该类药物治疗时应权衡利弊。SGLT-2 抑制剂的代表药物有达格列净、卡格列净、恩格列净等。目前,对 SGLT-2 抑制剂的相关研究大多集中在其对肾脏及 CVDs 保护作用方面。研究显示^[61],SGLT-2 抑制剂对患者的血压,尤其是收缩压有较好的控制效果。因此,SGLT-2 抑制剂可以减少患者因血压控制不良而导致 CVDs 或肾脏并发症的风险。Nauck MA 等^[62]也发现二甲双胍联合达格列净能明显降低收缩压,而且对体重也有明显的改善作用,

且有学者就推荐 65 岁以上的老年 2 型糖尿病患者使用此方案^[63]。二甲双胍联合 SGLT-2 抑制剂对糖尿病肾病的保护作用及机制仍有待阐明。

4 总结

二甲双胍是治疗 2 型糖尿病的基础和一线用药,应用广泛,其降糖、改善胰岛素敏感性以及控制体重的作用已得到临床上的认可。近年来,越来越多的新型糖尿病药物相继出现,2 型糖尿病的相关临床指南也越发重视多种药物的联合治疗,甚至是起始联合治疗。二甲双胍与其他类型的降糖药物的联合应用将长期是一个研究热点。目前的研究已发现二甲双胍与其他类型降糖药物联用在低血糖发生率、体重控制、血压及心血管保护方面等均有显著效果,临床上可根据患者的具体病情来制定个性化治疗方案,以达到更好的血糖控制及减少并发症。然而,当前关于联合用药的相关研究大多是联合用药对比单一用药,关于不同联合用药方案之间对比,包括预后改善、并发症管理、经济效益以及更多种药物联用的效果的对比有待在未来进一步探讨。

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