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Pyruvate Potential Effects on the Prevention and Treatment of Diabetes and Its Organ Complications

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Abstract: Pyruvic acid (pyruvate plus hydrogen [H^+]) is a key of important metabolites in glucose metabolism. Exogenous pyruvate can efficiently improve glucometabolic disorders: mainly preservation of anaerobic glycolysis in cytosol, reactivation of declined oxidative phosphorylation in mitochondria, hence, restoration of the aberrant Warburg effect, enhancement of redox potential status, inhibition of inflammation and apoptosis in addition to depression of advanced glycation end products (AGEs) in tissues. Therefore, pyruvate can protect against diabetes and its organ complications, turning the vicious cycle virtuous in diabetic initiation and development. Pyruvate advantages are incomparable to anions in current medical fluids and hold a potential paramount significance in clinical settings. This review illustrated pyruvate beneficial biomedical properties and their effects on the prevention and treatment of diabetes and diabetic organ complications with the experimental evidence and clinical case reports. It highlights the novel possibility to deal with diabetes by oral pyruvate, the superior choice to resuscitate critical care patients with or without diabetes by pyruvate-enriched fluids and the feasibility to prevent and treat diabetes and its complications with pyruvate-enriched oral rehydration solutions (Pyr-ORS) as a functional beverage in a large population. Attention must be paid to diabetes research with pyruvate and its clinical trials are urgently warranted.

Keywords: Pyruvate, Diabetes, Diabetic Organ Complications, Glucose Metabolism, Oral Rehydration Salt

丙酮酸钠在防治糖尿病及器官并发症中的潜在作用

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摘要：丙酮酸(Pyruvic acid: 丙酮酸根+氢离子)是糖代谢中的关键重要中间产物，外源性丙酮酸盐(Pyruvate)能有效改善糖尿病的糖代谢紊乱，主要是维持胞浆中的无氧糖酵解，逆转线粒体中受抑制的氧化磷酸化过程，从而改善Warburg effect的异常代谢，并提高氧化还原势能，抑制炎症反应和细胞凋亡，还阻止糖基化终产物(AGEs)的组织沉着。因此，它能有力改善糖尿病和其器官并发症发生发展中的恶性循环。丙酮酸盐的优异特性是现有医用溶液中阴离子所不及的，具有重大潜在临床应用价值。本文综述外源性丙酮酸钠的主要生物学特性和其对糖尿病的防治作用，及相关动物和临床证据，说明口服丙酮酸钠(Sodium Pyruvate)可能为糖尿病的防治提供新的途径；无论是否糖尿病患者，含丙酮酸钠的静脉或口服溶液可能是危重病救治中的最佳选择；以及，口服经丙酮酸钠口服补液盐(Pyr-ORS)制备的功能性饮料

可望用于大规模人群防治糖尿病及器官并发症的可行性。丙酮酸钠用于糖尿病防治应得到切实的关注和深入研究，已有必要和条件开展相关临床对照试验。

关键词：丙酮酸盐，糖尿病，糖尿病器官并发症，口服补液盐，糖代谢

1．前言

丙酮酸(Pyruvic acid)是哺乳类动物和人体内糖代谢的关键中间产物，是连接三大物质：糖，脂肪和蛋白质的枢纽，位于葡萄糖的无氧酵解和有氧氧化代谢的连接处，因此，对周身的代谢都有密切关联。糖尿病是糖代谢混乱的周身疾病，其发生发展和胰腺中胰岛细胞功能不全，胰岛素分泌绝对或相对不足有关，但也和各组织细胞的胰岛素受体功能下降及糖代谢紊乱的产物造成的细胞代谢多样改变有关，各种成因间的作用导致恶性循环而造成多器官的并发症，主要是肾脏，眼睛，脑和周围神经，心脏，以及皮肤等糖尿病性损伤。但是，糖尿病及器官并发症不会仅依赖给与胰岛素而阻止疾病的发展，更不能使其逆转。半个多世纪前就发现糖尿病患者体内存在丙酮酸盐/根(Pyruvate)代谢紊乱[1,2]，因此，外源性丙酮酸盐在体内的代谢和糖尿病的防治有着密切关系[3]。尽管临床上尚无可供应用的产品，本文讨论外源性丙酮酸钠盐(Sodium Pyruvate: SP)对糖尿病及器官并发症可能的潜在防治作用。

2．丙酮酸盐优异的生物学和药理学特性

丙酮酸根阴离子具有众多优异的特性，是现有医用溶液中的阴离子：重碳酸氢盐，乳酸盐，醋酸盐，枸橼酸盐，葡萄糖酸盐，甚至苹果酸盐及氯离子所远不及的[4]，相关内容已有介绍[4,5]，其和防治糖尿病有关的要点如下：

2.1．提高细胞在无氧或缺氧下的耐受性

丙酮酸根是糖无氧酵解的中间产物，外源性丙酮酸盐也同样能在无氧条件下，无需能量供给自发地在乳酸脱氢酶(LDH)的作用下，还原成糖酵解的终产物：乳酸盐，同时，这反应必然偶联着还原型的尼克酰胺腺嘌呤二核苷酸(NADH)氧化成氧化型(NAD^+)，从而提高了NAD^+/NADH之比，这一高比值是糖酵解在3-磷酸甘油醛脱氢酶(G-3PD)一步代谢所必须的。此外，它也促进糖酵解过程中的限制酶，如受高糖抑制的丙酮酸激酶(PK)的活性[3]，因此，外源性丙酮酸盐能有效增进受多种病因(如缺氧/缺血，创伤，败血症和高糖等)所致而抑制的糖酵解过程，从而维持了‘糖酵解-ATP’(glycolytic ATP)的生成，供维持细胞基本结构和功能，如细胞膜结构，膜两侧离子梯度和钠-钾泵活性等所需[6,7]。更重要的是外源性丙酮酸盐经线粒体内膜的载体与氢离子(质子[H^+])同相转运入线粒体后，能在无氧下逆转(经PI3K信息途径，待发表资料)受多病因损伤而抑制的氧化代谢关键酶：丙酮酸脱氢酶(PDH)复合体的活性，这是丙酮酸盐直接作用于异常增高的PDH激酶(PDK：NADH升高是PDK增强的重要因素之一), 抑制PDK磷酸化的结果，从而活化PDH，即PDH磷酸化受抑制(非磷酸化PDH才有活性)[3]。早已明了，类同于二氯乙酸(DCA)，丙酮酸盐也属于PDH刺激剂[3,6], 还增强丙酮酸羧化酶(PC)活性[5]，因此，能在低氧下恢复氧化代谢，经乙酰辅酶-A和三羧酸循环(TCA cycle)生成‘线粒体-ATP’(Mitochondrial ATP)，恢复糖的正常代谢和能量供应。所以，外源性丙酮酸盐能在无氧下维持糖酵解，缺氧下恢复细胞糖的能量代谢。关于前者，至今有三个著名的动物实验可以论证：预先接受无氧暴露的大鼠给于丙酮酸盐，脑内ATP含量较多，生存延长；无氧下含丙酮酸盐培养的肝细胞生存延长，以及红细胞在含有丙酮酸盐的体外循环中维持ATP生成量和ATP酶活性[8-10]。关于后者也早有多个体内外实验证实[11,12]，新近，在高糖下又获得恢复PDH活性的证据[3]。另外，丙酮酸盐能直接刺激缺氧诱导因子-1(HIF-1)的活性，激活HIF-1-促红细胞生成素(HIF-1-EPO)通路，进一步刺激下游的多个糖代谢有关酶活性[13,14]。其次，它还能竞争性抑制异常增强的醛糖还原酶(AR)活性，抑制亢进的山梨醇支路[3,15]，应被称为一种新的AR抑制剂，AR抑制剂在临床上已明确特别适用于糖尿病器官并发症的防治[16]；它也增强受抑制的6-磷酸葡萄糖脱氢酶(G-6-DP)活性，共同促进磷酸戊糖支路[17]，改善谷胱甘肽还原型/氧化型(GSH/GSSG)比例。所以，它能全面纠正糖的异常代谢，并改善氧化还原势能，集中表现在逆转异常的所谓糖尿病‘假性缺氧’，即本质上的Warburg现象(Warburg effect: 有氧条件下异常增多的乳酸生成和氧化代谢的抑制，如见于多种危重病，糖尿病，肿瘤和老龄化等[3,18])。

2.2．纠正缺氧型乳酸性酸中毒

丙酮酸盐在LDH的还原反应中偶联的NADH氧化过程中，自发地吸收消耗了一个胞浆中的[H^+]，生成了乳酸和NAD^+，这反应在全身细胞内发生。因此，丙酮酸盐的LDH还原反应是周身的碱化反应，有利纠正细胞内的酸化[19]；这与乳酸盐的氧化反应正相反：导致细胞的酸化。其次，在线粒体经PDH在TCA cycle糖的氧化磷酸化代谢中，也消耗[H^+]。因此，丙酮酸盐无论经还原或氧化反应都等分子量地消耗[H^+]。再者，在胞浆的糖原异生过程中，来自丙酮酸盐生成的糖原过程中还要等分子量地消耗[H^+]，而在由乳酸盐生成的糖原中，则没有消耗更多的[H^+]，因为，在乳酸盐的LDH氧化反应中已释放出相应的[H^+]。总之，丙酮酸盐具有特异的纠酸功能，能在无氧下维持关键的糖酵解代谢步骤，在缺氧下有效纠正缺氧型乳酸性酸中毒[4,7]，已有多个动物体内实验论证[20-23]。理论上，同样适用于纠正糖尿病酮症酸中

毒[7]，但尚缺乏实验证据。有关外源性丙酮酸盐在细胞内的代谢途径详见已有报道的图解[3-5,7]。

2.3．抗氧化应激和炎症

丙酮酸盐还是强有力的天然抗氧化剂和抗炎剂。它能在无需能量代谢下自发地和氧/氮自由基反应，生成水，二氧化碳或乙酸，消除体内的氧化应激状态[24]；并能抑制多种炎症因子的分泌和激活，降低组织中炎症反应和炎症细胞的浸潤[21,25]。这显然阻碍了糖尿病器官并发症发生和发展中的一个重要环节[3]。

2.4．保护线粒体结构和功能及抗细胞凋亡

丙酮酸盐在包括高糖等多种致病因素作用下有助维持线粒体的结构和功能，并抑制细胞凋亡过程[26,27]；而线粒体损伤是糖尿病器官并发症发病和发展的又一重要特征与环节，其损伤/裂变和能量学与自噬的异常是器官病变的早期表现[28,29]。然而，证据表明丙酮酸盐有效保护了高糖和糖尿病下的线粒体能量代谢，抑制内浆网应激和细胞凋亡[3,27]。

可见，丙酮酸盐具备的特性是现有治疗溶液中阴离子所无力媲美的，它是至今了解唯一具备以上多功能特性的阴离子，用它取代更新现有溶液中的阴离子，创新为含有丙酮酸钠的盐水，丙酮酸钠林格氏液，或丙酮酸钠口服补液盐等用于危重病的救治[10,18]，将可防治常规溶液导致的毒性副作用：医源性复苏损伤(如生理盐水造成的高氯性酸中毒和肾功能损害；乳酸/醋酸钠林格氏液可导致的乳酸性酸中毒，及其周身炎症反应等)，并保护多器官功能。含丙酮酸钠的溶液(包括晶体和胶体)不仅是血容量扩充剂，同时也是器官功能不全和酸碱失衡的治疗剂[30,31]，而这对糖尿病患者更有重要意义，可望明显提高危重病救治的成功率和生存率。

3．丙酮酸盐防治糖尿病及器官并发症的证据

3.1．动物实验

早在上世纪90年代就有动物体内外实验结果显示：外源性丙酮酸盐和内源性的一样有效对抗氧化剂的作用，保护在高糖和糖尿病下的大鼠眼角膜的白内障病变[32,33]，以后发现不仅有预防作用，更在发生糖尿病性白内障后，它能缓解AGEs的沉淀，并阐述了生化反应过程[34,35]。

10多年前，国内也有口服丙酮酸盐抑制糖尿病性白内障的实验报道，并首先初步发现有效治疗大鼠糖尿病性视网膜病变[36,37]，此后得到进一步证实[38,39]。不仅口服有效，仅用局部滴眼剂在人体也应有效[40]。

在动物胰岛细胞的移植中早已发现，丙酮酸盐有效保护胰岛细胞的生存和功能[41,42]。人体胰岛细胞在丙酮酸盐的培养下能延长生存[43]。最近的小鼠实验结果表明：在危重病时，丙酮酸盐有保护胰岛β细胞功能不全的功用[44]。细胞外的pH值能影响胰岛细胞的胰岛素分泌和糖代谢，而移植的胰岛内pH值下降[45,46]；同时，葡萄糖不耐受状态和糖尿病病变使胰岛组织血流分布异常，糖尿病大鼠的胰岛组织血流量下降[47,48]。然而，初步实验资料表明，丙酮酸盐而不是乳酸盐能增加移植胰岛的血流量[49]；此外，反复证实丙酮酸盐能有效提高休克或创伤动物细胞内pH和内脏血流量[50,51]。这些都强烈提示口服丙酮酸盐能改善糖尿病患者胰岛组织可能存在的pH和血流量下降，有助促进胰岛素分泌[52]。近来的体外人体肾小管上皮(HK-2)细胞和动物体内实验，首次显示高糖下丙酮酸盐有效保护肾细胞，提高体内胰岛素水平，防治糖尿病肾病：糖尿病状态好转；肾功能和病理改变异常都有缓解[3, 27]，与糖尿病眼病防治效果一致。

尽管至今尚无研究报道丙酮酸盐对糖尿病的其他主要器官并发症：脑，心和皮肤病变的作用，但是，现有认识强烈提示丙酮酸盐也应对糖尿病性脑和周围神经病变，心肌病变及糖尿病皮肤溃疡及烧伤皮肤的愈合等有良好的功效。糖尿病性脑病有脑内乳酸盐的异常升高，而乳酸盐和丙酮酸盐有着根本相反的生化反应和病理生理作用；糖尿病是老年性痴呆的重要病因，糖尿病性老年痴呆也有明显的脑内AGEs沉着，而丙酮酸盐对此有抑制作用[53-55]。DCA能经刺激PDH活性，促进氧化代谢而改善糖尿病心肌病变[56]，而丙酮酸盐也是心肌病变PDH刺激剂[5,57]。以上病变：AGEs生成和组织沉着及PDH活性表达下降也同样存在于糖尿病性皮肤损伤[58,59]。至今，尚无丙酮酸盐溶液在糖尿病动物复苏及酮症酸中毒模型中作用的报道，但初步表明它能在危重病复苏动物中保护胰岛β细胞及抑制高血糖作用[44]。

3.2．临床报告

在临床上，已有个案报道分次口服大剂量(30-60克/日)丙酮酸钠共7-10天，使6例1型糖尿病患者餐后血糖有明显下降趋势，一周后出现临床低血糖症状，其中4例必须减少每天的胰岛素用量。血浆丙酮酸盐水平升高和单次口服摄入剂量有关，这和静脉给药类似。副作用仅胃肠道刺激症状：肠鸣，气胀和腹泻等，单次口服10-15克则多无明显副作用[60]。此后的一例线粒体病性的糖尿病者测定了血胰岛素水平，每日胰岛素用量从32单位下降到20单位，认为口服大剂量丙酮酸钠能促进胰岛素分泌[61]。此外，口服大剂量丙酮酸钠可能提高血浆胰岛素水平也见于非糖尿病患者[62]；口服大剂量丙酮酸钠甚至改善先天性的线粒体病[63]。

以上资料强烈表明丙酮酸盐在临床上用于防治糖尿病及器官并发症的可能性，它作用于糖尿病及器官并发症发生和发展过程主要机理中的多个环节：改善和保护胰岛组织血流量和β细胞功能，促进胰岛素分泌，提高血浆胰岛素水平；同时改善糖代谢紊乱的多个途径：尤其是逆转关键的PDH抑制和Warburg现象；抑制氧化应激-炎症反应，提升氧化还原势能，保护线粒体和内浆网功能，阻止细胞凋亡，并缓解和逆转AGEs的生成和组织内沉着。因此，有望改变发病机理中的恶性循环成良性循环[3]，为此，深入开展相关动物体内外实验研究和临床对照试验实属必要。

4．丙酮酸钠防治糖尿病临床应用的可行性

尽管多个小规模临床试验表明大剂量静脉注射丙酮酸钠，甚至耐量试验(4-10分钟内注10克)和口服都显示有效，无毒，安全性高，对人体无害[1,64,65]；临床病例报告提示口服大剂量丙酮酸钠有望治疗糖尿病，但是，实际上大剂量口服丙酮酸钠仍因明显的胃肠道刺激而无法推广[60]；而小于10-25克/日并无明显临床作用[66,67]。为此，我们在2012年革新了世界卫生组织倡导的，建立在胃肠道上皮细胞存在‘钠-糖共同转运体’理论基础上开发的口服补液盐(WHO-ORS)，创新了丙酮酸钠口服盐(Pyr-ORS)[18,50]。含小剂量丙酮酸钠(3.5g/L)的Pyr-ORS，因同时含有适量的糖而有利丙酮酸盐的吸收，在动物大出血或烧伤休克的胃肠道复苏中显著保护多器官功能，并快速纠正严重代谢性酸中毒，延长生存期[23,51]；Pyr-ORS同样能有效缓解糖尿病和其肾病并发症[3]。丙酮酸钠有效作用于糖尿病的异常糖代谢，为其防治提供了新的观点和途径：除了常规的饮食控制，补充胰岛素或胰岛素分泌刺激剂(改善β细胞对促分泌物质应答缺陷)，减肥与运动和新的胰岛β/α细胞受体激动剂：胰高血糖素样肽-1(GLP-1)及尿排糖药物：钠-糖共同转运体-2(SGLT-2)抑制剂外，增添了逆转糖代谢异常和促进糖的氧化代谢的新疗法。因此，口服Pyr-ORS可望取代大剂量单纯的丙酮酸钠制剂，发挥临床疗效。稍加调节Pyr-ORS的配方，可以制备成含丙酮酸钠的功能饮料，可能为用于大规模人群中糖尿病及器官并发症的防治提供可行途径。

理论上，含丙酮酸钠的创新溶液应是糖尿病患者合并急性创伤如出血，烧伤和败血症等危重病的液体治疗中静脉输液的首选[5,10,30,31]，因它具有超越常规阴离子保护细胞代谢的优越性，这无论对糖尿病患者或无糖尿病合并者都有重要临床意义；对糖尿病酮症酸中毒而言，推测丙酮酸钠溶液显然优于生理盐水，甚至用于慢性肾病，尤其是糖尿病肾病末期的腹膜(包括血液)透析液，也应改用含丙酮酸钠的透析液[15,22]，这些尚需深入的实验观察。尽管临床上尚无相应产品，但在临床试验中可于临用前即时配置[68]；丙酮酸盐研究领域中的资深团队也积极提倡开展丙酮酸钠溶液休克复苏的临床应用[69]。关于丙酮酸钠水溶液长期稳定性和可能的体内细胞毒性问题已基本阐明，是可克服的[70]；至今，尚无丙酮酸钠临床试验的毒性报道，也无其二聚体的体内毒性证据[71]。此外，丙酮酸盐中以钠盐为佳，因为，人体中钠盐含量高，无论口服或输注钠盐才适用于临床普遍应用。虽然，国内外都有动物实验报道口服丙酮酸钙的疗效[72]，但钙盐水溶性甚差，不易吸收；人体实验也无效果[73]。至于丙酮酸锂，尽管它也显示细胞保护作用[74]，但锂盐同样不适宜临床的普遍需要。

最后，近20年来也有多个报道显示丙酮酸盐的酯类衍生物：丙酮酸乙酯(Ethyl Pyruvate, EP)有良好的糖尿病及其器官并发症的防治作用[75-77]，这进一步支持了外源性丙酮酸钠盐的潜在临床应用价值。虽然，EP在众多动物实验中显示了优越性，但是，EP与SP仍有本质上的不同，它不是纠酸制剂，在人体并无疗效[18,70]，首个EP的二期临床试验也早在10年前宣告失败[78]，证实了它的研究确有生物学价值，但并无临床应用前景。此外，尽管DCA对实验性糖尿病也有一定疗效，但临床毒性较大，它防治缺氧型乳酸性酸中毒的临床试验也早告失败[79]，提示丙酮酸钠的临床应用有不可取代的重大**意义**。

5．结论

众多证据表明丙酮酸钠可能有效防治糖尿病及其常见器官并发症，它作用于糖尿病发生发展机理的多个环节，重要的是能活化受抑制的糖代谢关键酶PDH的酶活性和消除Warburg现象的异常代谢，有望逆转病变的恶性循环发展；为糖尿病的防治提供了新的思路。口服的丙酮酸钠溶液可经改造制备成含丙酮酸钠口服补液盐(Pyr-ORS)的饮料，用于大众防治糖尿病和器官并发症。糖尿病患者的静脉液体治疗应以含丙酮酸钠的溶液为优，临床上虽尚无可供应用的产品，但开展相关临床试验仍然必要和可行。丙酮酸钠的潜在临床适应症宽广，应用意义重大，尤其对糖尿病患者而言，值得大力开展深入的实验观察和临床研究。

说明

本文内容和观点不代表 Fresenius Medical Care, USA 的意见。本文并未接受任何方来源的资助。

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