中西医结合诊治糖尿病

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摘要 糖尿病及其慢性并发症严重威胁着人类健康, 给全球带来巨大经济负担。自20世纪70年代以来众多研究者采用中西医结合的方法对糖尿病及其并发症进行了研究, 取得了一定的成就, 为证实该领域中医药所发挥的作用提供了客观依据。本文针对中西医结合诊治糖尿病及其并发症的研究进行了综述。

关键词 中西医结合, 糖尿病, 血瘀证, 糖尿病并发症

糖尿病是常见的慢性疾病, 严重威胁着人类健康, 给全球带来了巨大的经济负担。据国际糖尿病联盟2019年发布的第九版全球糖尿病地图显示, 目前全球约4.63亿人患有糖尿病, 预计到2045年这一数字将会达到7亿, 全球每年的糖尿病相关医疗开支约为7600亿美元, 约有420万人死于糖尿病或其并发症, 约占全球全死因死亡的11.3%^[1]。中医认为糖尿病属于“消渴”“消瘴”等范畴, 早在《黄帝内经》中就有相关记载。历经2000余年, 中医历代医家对“消渴病”的认识逐渐成熟和完善。自20世纪70年代以来, 众多研究者采用中西医结合的方法对糖尿病及其并发症进行了研究, 取得了一定的成就。本文针对中西医结合诊治糖尿病的研究进行了综述。

1 糖尿病血瘀证的中西医结合研究

消渴与血瘀相关的论述自古有之, 《灵枢·五变

篇》中曾记载:“血气逆留, 髓皮充肌, 血脉不行, 转而为热, 热则消肌肤, 故为消瘴”, 提示瘀血可能是导致消瘴的病因。《金匱要略》曰:“病者如热伏, 烦满, 口干燥而渴, 其脉反而无热, 此为阴伏, 是瘀血也”; 唐容川《血证论》曰:“瘀血在里则口渴, 所以然者, 血与气本不相离, 内有瘀血, 故气不得通, 不能载水津上升, 是以为渴, 名曰血渴, 瘀血去则不渴矣”等记载对瘀血所致烦渴的症状特点进行了描述。

在前人有关消渴与血瘀的论述基础上, 20世纪70年代北京协和医院祝谌予教授^[2,3]结合自身临床观察, 发现许多糖尿病患者存在血瘀症状和体征, 1978年正式提出了糖尿病血瘀证的学术思想, 并报道了用活血化瘀法治疗糖尿病的临床病例, 通过对110例糖尿病患者的临床症状和体征进行辨证分型, 发现糖尿病临床虽可分为阴虚、气阴两虚、阴阳两虚、血瘀等不同证型, 但血瘀证可存在于临床各型之中^[4], 引起了国内同行的高度重视。其团队采用中西医结合方法开展糖

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尿病血瘀证的临床研究,发现糖尿病血瘀证患者存在血液流变学异常,包括全血黏度、血浆黏度增高,红细胞变形能力下降,体外形成血栓的湿重显著增加,红细胞形态异常比例明显高于正常对照人群,下肢痛及足痛患者小腿血流量减少,足病患者减少更为显著.血瘀证患者血浆血栓素 $B_2(TXB_2)$ 水平升高、6-酮-前列环素 $F_{1\alpha}(6\text{-Keto-PGF}_{1\alpha})$ 水平降低, $TXB_2/6\text{-Keto-PGF}_{1\alpha}$ 升高,红细胞超氧化物歧化酶(RBC-SOD)、血清丙二醛(MDA)、 Na^+-K^+-ATP 酶、 $Ca^{2+}-Mg^{2+}-ATP$ 酶活性下降^[5-11].进一步研究发现,益气养阴活血方(由生黄芪、生地、苍术、元参、丹参、葛根、广木香、当归、益母草、赤芍、川芎组成),能够减轻气阴两虚血瘀型糖尿病患者的临床血瘀征象,调节血糖、血脂代谢,改善全血黏度、血浆黏度、红细胞聚集、红细胞变形能力等血液流变学指标^[8-12].以上研究为糖尿病血瘀证提供了客观依据及治疗方法,并发现糖尿病患者在临床血瘀证出现之前就有血液流变学异常,提出血瘀证可能贯穿于糖尿病的始终,要尽早应用活血化瘀药物以“未病先防、既病防变”的治疗思路.

在此理论的影响下,国内先后开展了应用清热活血、益气养阴活血、化痰活血等方法治疗糖尿病及其慢性并发症的中西医结合研究.郭赛珊等人^[9,10]通过随机对照临床试验观察到益气养阴活血方不仅能改善气阴两虚血瘀型2型糖尿病患者的临床症状,而且可以降低空腹血糖及餐后2小时血糖,优于安慰剂组($P<0.05$),后续研究发现该方还可部分延缓或逆转糖尿病前期患者转化为糖尿病^[13].陈宽生等人^[14]发现清热活血法可有效改善2型糖尿病患者症状;应用益气养阴活血法治疗2型糖尿病,能够显著减轻患者临床症状,改善血糖、血脂以及全血黏度、红细胞聚集指数等反映血液流变学的指标^[15];利用化痰活血法可明显降低肥胖型2型糖尿病患者空腹及餐后2小时血糖、糖化血红蛋白、胰岛素抵抗指数,增高胰岛素敏感性,降低全血黏度及纤维蛋白原^[16].杨明会等人^[17]选择气虚血瘀证的老年2型糖尿病患者60例,随机分为两组,单纯西药对照组30例,进行常规基础治疗,试验组30例,在常规降糖西药治疗的基础上加用保元活血颗粒,共治疗2个月,发现试验组总有效率为90%;对照组总有效率为50%;两组总有效率比较差异有显著性($P<0.01$).

2 糖尿病治疗的中西医结合研究

中医药治疗糖尿病历史悠久,但是疗效方面多关注于多饮、多尿、多食、消瘦等症状改善情况.通过中西医结合临床随机对照研究,采用空腹及餐后血糖、糖化血红蛋白、胰岛素水平、血糖达标率等客观指标逐步为中药治疗糖尿病及糖尿病前期提供客观证据.倪青等人^[18]将糖尿病前期患者116例,按2:1比例分为中药组、对照组,两组患者均予适当控制饮食、健康教育、运动等一般治疗,中药组在此基础上口服芪药消渴胶囊,发现两组患者空腹血糖(fasting blood glucose, FBG)、餐后血糖(postprandial blood glucose, PBG)、糖化血红蛋白(HbA1c)治疗后均较治疗前下降($P<0.05$, $P<0.01$),但两组间比较差异无统计学意义.中药组2 h胰岛素较治疗前下降,与对照组比较差异有统计学意义($P<0.05$),疗程结束及随访中药组复常率优于对照组($P<0.05$).张学红等人^[19]将172例患者随机分为治疗组和对照组.治疗组口服消糖平胶囊,每次3粒,每日3次,二甲双胍每次0.25g,每日2次;对照组服用同等剂量的二甲双胍,治疗后两组FBG, 2hPBG, HbA1c均降低($P<0.05$ 或 $P<0.01$),且两组治疗后组间比较,治疗组明显低于对照组($P<0.05$).

近年来一些多中心随机对照试验(randomized controlled trial, RCT)为中药治疗糖尿病提供了高质量循证医学证据.在5个中心对400名糖尿病患者进行为期12个月的治疗,之后又再进行了12个月的随访,与安慰剂组相比,金芪降糖片组从糖尿病前期转变为糖尿病的风险低0.58倍(HR(95%CI): 0.58(0.384, 0.876), $P=0.010$).ITT分析显示,金芪降糖片组完成治疗后的糖尿病发生率为16.5%,而对照组为28.9%.金芪降糖片组在接受12个月干预后血糖正常的患者百分比为41.8%,而对照组为27.8%.提示金芪降糖片可能是预防性治疗2型糖尿病的有效干预措施^[20].另一篇为期12周80名受试者参与的RCT研究表明中药乌梅丸在降低空腹和餐后血糖水平及HbA1c方面无显著差异^[21].一项多中心、随机双盲、平行对照临床研究发现96例稳定服用二甲双胍血糖仍不达标的2型糖尿病患者联合应用津力达颗粒使用2周后可使HbA1c降低0.92%(安慰剂组HbA1c降低0.53%),并能改善胰岛素抵抗,提高胰岛素敏感性及 β 细胞功能指数^[22].480例初发2型糖尿病患者的多中心、随机双盲、安慰剂平行对照

临床研究发现糖敏灵丸干预12周后, HbA1c可降低1.03%, 并能降低患者体重、身体质量指数(body mass index, BMI)及腰围^[23]。桑枝总生物碱片IIIa期临床试验是与西药(阿卡波糖)头对头比较的随机双盲研究, 由北京协和医院梁晓春牵头, 中国23家临床机构共同参与完成, 共入组病例600例(桑枝总生物碱组360例, 拜唐苹240例), 研究结果显示桑枝总生物碱可降低糖化血红蛋白0.93%, 糖化血红蛋白达标为47.7%, 与西药对照药相当, 但胃肠不良反应减少近1/2^[24]。

3 糖尿病慢性并发症的中西医结合研究

糖尿病周围神经病变(diabetic peripheral neuropathy, DPN)是糖尿病常见并发症之一, 属于中医消渴病兼证范畴, 但目前尚缺乏有效的改善手段。梁晓春课题组^[25]于20世纪90年代即提出DPN的核心病机是“肾虚血瘀、筋脉痹阻”, 可采用补肾活血温经法治疗DPN的学术观点。通过对192例2型糖尿病患者测定交感神经皮肤反应(sympathetic skin response, SSR)及传导速度分布(conduction velocity distribution, CVD)范围, 在国内率先发现血瘀与阳虚等证候与CVD, SSR等电生理指标具有相关性, 随病程延长血瘀证、阳虚证积分均显著增高。临床实验证实, 补肾活血温经中药可以改善DPN患者神经电生理指标, 改善周围运动神经波幅、尺神经的运动神经传导速度, 增加SSR波幅, 改善麻木、怕凉、无力、疼痛等肢体症状, 改善DPN患者红细胞山梨醇浓度、醛糖还原酶(AR)活性及 $\text{Na}^+ - \text{K}^+$ -ATP酶活性; 而且对于患者的肝肾功、血常规等无影响, 服药期间无明确不良反应^[26,27]。实验研究发现, 补肾活血温经中药能够改善糖尿病大鼠行为学异常, 改善链脲佐菌素诱导的糖尿病大鼠(STZ-DM)的痛阈值, 增快STZ-DM大鼠坐骨神经传导速度, 进一步行光镜检查可见坐骨神经超微结构的改善。同时改善糖尿病大鼠近端胃排空异常, 减轻糖尿病大鼠胃自主神经病变。本课题组对补肾温经活血法治疗DPN的机制也进行了进一步研究, 从整体、细胞及分子水平上研究了补肾活血温经法对多元醇通路、糖基化终产物(AGEs)、神经营养因子、氧化应激、自噬及神经修复再生功能的影响, 证实了“补肾活血温经法”可通过上述途径对DPN起到治疗作用^[28-31]。另有研究者对益气活血、通络止痛中药木丹颗粒治疗DPN的研究综

述, 发现该药亦对神经传导速度、神经形态学、代谢及氧化应激等方面具有影响^[32]。此外, 有研究者发现复方芍药胶囊对糖尿病大鼠体重或血糖水平无明显影响, 但可显著改善机械性痛觉过敏、热痛觉过敏和神经传导速度, 保持髓磷脂和轴突结构的完整性, 这些作用可能与下调坐骨神经组织中凋亡相关蛋白的表达, 降低AGEs和一氧化氮合成酶(NOS)水平, 并增强血清中的抗氧化酶SOD活性有关^[33]。

2型糖尿病患者轻度认知功能障碍(高达60%)和痴呆(50%~100%)发生率显著升高^[34]。然而目前糖尿病相关认知功能障碍发病机制尚未完全阐明。近年来研究提示氧化应激、神经炎症反应、下丘脑-垂体-肾上腺皮质轴功能亢进、 $\text{A}\beta$ 沉积和tau蛋白过度磷酸化、内质网应激、自噬、血脑屏障通透性增加、神经元凋亡等多种病理过程参与其中, 临床缺乏有效的治疗药物。糖尿病相关认知障碍属于中医消渴病兼证范畴。古人散在描述消渴呆病多从“肾虚、肝郁、痰”等方面论治。现代研究者主要围绕毒、瘀、脾阴虚、心等方面展开系列研究^[35-37]。临床研究证实脑复聪能有效改善辨证分型证属脾肾亏虚、痰浊血瘀的轻度认知功能障碍患者的认知功能^[38]。实验研究表明补肾活血方、脑复聪方可以改善缺血再灌注脑损伤小鼠学习记忆功能, 减轻海马神经细胞凋亡^[39-43]; 抑制体外培养的海马神经元及神经胶质细胞经炎症反应、内质网应激、海马神经元凋亡等途径对糖尿病相关认知功能障碍起到治疗作用^[44-46]。石杉碱A是一种从中草药青苔石杉中提取的生物碱, 是一种特异性可逆的乙酰胆碱酯酶抑制剂, 其能改善高脂诱导肥胖小鼠的物体识别能力和空间记忆, 上调皮质中的胰岛素和磷酸化的Akt水平, 降低了皮质 β -分泌酶(BACE1)的表达^[47]。黄芪多糖可降低STZ诱导的糖尿病大鼠的空腹血浆葡萄糖水平和体重, 改善认知能力, 减少海马CA1区的死细胞数量, 上调了CREB, NMDA和CaMK II的磷酸化水平^[48]。

糖尿病肾病(diabetic kidney disease, DKD)在中医中属于消渴肾病范畴。梁晓春课题组通过基础研究证实中药复方菟箭合剂可以显著降低单肾切除DKD模型鼠尿蛋白排泄量, 减轻肾小球肥大和肾小球细胞外基质增多的病理变化, 抑制肾小球系膜细胞表型转化, 抑制肾脏TGF- β 1的表达^[49], 抑制肾皮质蛋白激酶C途径的激活^[50]。体外实验证实菟箭合剂含药血清可

以抑制高糖环境培养的肾小球系膜细胞Akt(Thr308)的激活,提高Akt抑制物PTEN的活性^[51]。由于临床上DKD特征性表现为持续蛋白尿,而在治疗DKD大量蛋白尿时黄芪是最为常用的中药,且有大量的研究证实黄芪及其提取物可具有抑制DKD时肾脏的氧化应激、Akt激活和NF- κ B激活的作用,对DKD有很好的治疗效果^[52]。尹德海课题组^[53,54]研究证实黄芪菟箭合剂不仅能显著降低尿白蛋白排出率,还观察到能改善糖尿病大鼠的肾脏的病理改变,保护足细胞结构完整、减少足细胞足突分离,具有肾小球足细胞保护作用,机制可能与该药抑制PI3K/AKT通路及其相关的炎症反应有关。体外细胞培养实验也证实,黄芪菟箭合剂含药血清可抑制高糖培养下的系膜细胞增殖活性增加,降低细胞内COLIV, FN以及炎症因子的表达;可能与含药血清激活PTEN、抑制PI3K/AKT通路有关^[55]。黄葵胶囊已被中国国家食品药品监督管理局批准用于治疗肾脏疾病。多项随机对照试验的报道该药能使糖尿病肾病患者的蛋白尿显著降低,其机制可能是通过减少TGF- α , TGF- β 1表达和干预p38MAPK信号通路来改善肾脏的肾脏炎症损伤以及抑制ROS-ERK1/2-NLRP3炎性小体^[56]。杜仲可上调核因子 κ B相关因子2的表达,下调AGE受体的表达,即通过抑制AGEs的形成和RAGE的表达以及通过Glo1和Nrf2途径降低氧化应激,可改善糖尿病小鼠的肾脏损害^[57]。雷公藤及其提取物可减少尿蛋白并保护肾脏功能,它的药理机制涉及抗炎、抗氧化、抗肾小球硬化和抗纤维化,这是通过平衡Th1/Th2细胞,调节巨噬细胞浸润,调节p38MAPK, NF- κ B, TGF- β , Wnt/ β -catenin, Akt, Notch1, 上调自噬和下调 β -arrestin-1以及通过GSK3 β 依赖性机制增强肾小球足细胞中环孢素A的细胞骨架稳定活性等途径来实现^[58-60]。

4 总结与展望

1976年,北京协和医院在全国率先成立了中西医结合治疗糖尿病专科门诊,特请中华医学会糖尿病分会创办人、第一届主任委员池芝盛教授和名老中医祝谌予教授共同出诊,开启了中西医结合诊治糖尿病的新模式。采用中西医结合的思想和方法研究中医药诊治糖尿病及其慢性并发症自20世纪70年代以来持续至今,研究设计日趋成熟完善,研究成果逐步为世界所接受,为挖掘中医药宝库提供了崭新的途径。

然而,当前仍有多数实验研究仅限于应用现代医学的指标验证中医药的作用靶点,在机制探索方面尚缺乏创新性。目前降糖中药(或有效成分、或单体)的筛选模型常常局限于现有西药已知的治疗途径,反而一些常用西药降糖药物的发现却源自某些草药和植物。例如,二甲双胍的发现与山羊豆(*Galega officinalis*)这种传统草药有关^[61],钠-葡萄糖共转运蛋白-2抑制剂被法国化学家Petersen C偶然在苹果树的树皮中发现^[62]。中医药的宝库值得深入挖掘,今后对于已被临床研究证实的确实有效的中药方药(或单有效成分、或单体)的机理研究过程中应通过中西医结合的思想和方法,大胆尝试探索糖尿病新的治疗靶点和新的机制途径。

此外,糖尿病及其并发症方面临床研究虽然已开展众多多中心RCT研究,但研究多以实验室指标等替代结局为主要疗效评价标准,研究周期相对较短,尤其是糖尿病慢性并发症方面,经得起循证医学检验的研究结果尚不充分。因此,今后中西医结合糖尿病及其慢性并发症的临床研究尚需开展以生存率、心脑血管事件、生活质量等患者-重要结局为终点事件的高质量研究。

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Diagnosis and treatment of diabetes mellitus with integrated traditional Chinese and western medicine

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Diabetes and its chronic complications pose a serious threat to human health and impose a huge economic burden on the world. Under the guidance of the Communist Party of China after the founding of China, many scholars have studied diabetes and its complications by integrated traditional Chinese and western medicine since the 1970s, and made certain achievements, providing an objective basis for confirming the role played by traditional Chinese medicine in this field. This article reviews the research on the diagnosis and treatment of diabetes mellitus and its complications by integrated traditional Chinese and western medicine.

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