



· 专家述评 ·



童南伟，主任医师，教授，博士生导师，四川大学华西医院内分泌科执行主任。现任中华医学会内分泌学分会副主任委员、中华医学会内分泌学会糖尿病学组组长及肥胖学组副组长、四川省医学会内分泌及糖尿病专业委员会主任委员、四川省医师协会内分泌代谢医师分会会长。现为中华医学会医疗事故鉴定专家库专家、国家卫生健康委合理用药专家委员会内分泌代谢专家组专家、国家卫生健康委医师定期考核专家委员会内分泌代谢专家。致力于糖尿病、肥胖症、甲状腺疾病及内分泌代谢的疑难、少见罕见病的临床研究。参与制定国内多部糖尿病、甲状腺疾病等的诊治指南及专

家共识，在四川省开展了甲状腺疾病、碘摄入情况等多项研究。以主编或副主编身份参与制定国家统编教材、医学专著多部；以通信作者等在SCI收录期刊上发表论文70余篇。担任《中华内分泌代谢杂志》副总编，《中华糖尿病杂志》、《中国糖尿病杂志》、《中国实用内科杂志》等杂志编委。曾承担或正在承担获国家重大疾病新药创制计划、国家科技支撑计划、国家自然科学基金、卫生部青年基金、四川省重大科技基金多项重要科研项目。获得国家专利（共同发明）1项、四川省科技成果奖3项。

《肿瘤相关性高血糖管理指南（2021年版）》 解读

吴绮楠¹，童南伟²

1. 重庆医科大学附属大足医院（大足区人民医院）内分泌科，重庆 400030；
2. 四川大学华西医院内分泌代谢病科，四川 成都，610000

【摘要】 恶性肿瘤和糖尿病均已逐渐成为中国常见的慢性非传染性疾病，两者关系密切，糖尿病患者中多种恶性肿瘤的发生风险增加、致死率高、预后不良，肿瘤患者中血糖升高很常见。部分恶性肿瘤可导致高血糖和（或）糖尿病，恶性肿瘤的治疗（包括手术应激、化疗药物、放射治疗、糖皮质激素、多种靶向药物、免疫检查点抑制剂的应用等）过程中可能出现高血糖和（或）糖尿病，统称为肿瘤相关性高血糖。肿瘤相关性高血糖在临床上管理难度大，血糖控制情况的好坏与恶性肿瘤患病风险及不良预后密切相关，目前尚无相关的指南可用于指导临床诊治和管理。因此，恶性肿瘤相关性高血糖的规范化管理问题日益受到内分泌科及肿瘤科专家的重视，临床上也迫切需要就肿瘤相关性高血糖的管理进行规范化的指导。鉴于此，中国抗癌协会肿瘤内分泌专业委员会和重庆市中西医结合学会肿瘤内分泌分会综合国内肿瘤学和内分泌学多位专家的意见起草了《肿瘤相关性高血糖管理指南（2021年版）》。该指南除归纳和总结糖尿病与多种恶性肿瘤的关系，肿瘤导致高血糖和（或）糖尿病的病因，肿瘤相关性高血糖的流行病学，肿瘤相关性高血糖的概念，诊断和鉴别诊断标准外，还重点介绍了肿瘤相关性高血糖的规范化管理，包括肿瘤相关性高血糖的总体评估方法和原则，个体化控制目标，住院期间的管理（入院前准备，住院期间患者的血糖管理措施，胰岛素疗法，重症监护病房和非重症监护病房的管理，酮症酸中毒和高渗性高血糖状态，低血糖的处理，围手术期血糖管理，非进食肠内或肠外营养情况下血糖的管理，妊娠合并高血糖或糖尿病的管理，糖皮质激素的应用的管理，临终关怀，从住院到门诊的过渡，用药注意事项，出院前处理等情况），多种降糖药物对恶性肿瘤的影响，肿瘤治疗药物对血糖的影响和门诊期间的管理，包括恶性肿瘤患者档案的建

基金项目：国家科技部重大专项（2016YFC1303702）；重庆市科技局与卫健委联合中医药技术创新与应用发展资助项目（2020ZY013540）。

通信作者：童南伟 E-mail: tongnw@scu.edu.cn

立, 血糖及并发症相关问题的健康检查, 长期的随访和评估。此外, 结合中国医疗的实际情况, 指南针对肿瘤相关性高血糖患者的双向转诊和分级诊疗提出了相关建议和标准, 以利于各层级医疗机构和医务人员方便的执行。本指南对推荐意见根据循证医学证据等级分级原则提出了相应的分级, 将有助于临床医师对肿瘤相关性高血糖患者进行合理化和规范化的管理, 以期改善其临床结局和预后。现就该指南的内容和推荐意见做一解读。

[关键词] 肿瘤相关性高血糖; 管理; 指南解读

DOI: 10.19401/j.cnki.1007-3639.2021.12.002

中图分类号: R730.6 文献标志码: A 文章编号: 1007-3639(2021)12-1154-09

Interpretation of Guidelines for the Management of Tumor-associated Hyperglycemia (2021 edition) WU Qinan¹, TONG Nanwei² (1. Department of Endocrinology, Dazu Hospital of Chongqing Medical University, The People's Hospital of Dazu, Chongqing 400030, China; 2. Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, Chengdu 610000, Sichuan Province, China)

Correspondence to: TONG Nanwei E-mail: tongnw@scu.edu.cn

[Abstract] Malignant tumors and diabetes mellitus have gradually become the most common chronic non-communicable diseases in China. They are closely related. The risk, mortality and adverse prognosis of various malignant tumors in diabetic patients are significantly increased. Hyperglycemia in cancer patients is very common. From the aspect of etiology, some malignant tumors lead to hyperglycemia and/or diabetes, and hyperglycemia and/or diabetes can occur during the treatment of malignant tumors, including surgical stress, chemotherapeutic drugs, radiotherapy, glucocorticoids, a variety of targeted drugs and the application of immune checkpoint inhibitors, which is collectively referred to as tumor-associated hyperglycemia. Tumor-associated hyperglycemia is difficult to manage in clinical practice, and the quality of blood glucose control is closely related to the risk and adverse prognosis of patients with malignant tumor. However, there is currently no relevant guideline for the clinical diagnosis and management. Therefore, standardized management of malignant tumor-associated hyperglycemia is necessary. In view of this, the Onco-endocrinology Society of Chinese Anti-Cancer Association and Onco-endocrinology Society of Chong Qing Integrative Medicine Association have drafted Guidelines for the Management of Tumor-associated Hyperglycemia (2021 Edition), a comprehensive report based on the opinions of many domestic experts in oncology and endocrinology. In addition to summarizing the relationship between diabetes and multiple malignant tumors, the guidelines include the etiology of tumor-associated hyperglycemia/diabetes, the epidemiology of tumor-associated hyperglycemia, the concept of tumor-associated hyperglycemia, the diagnostic and differential diagnostic criteria and the standardized management of tumor-associated hyperglycemia, including the overall assessment methods and principles of tumor-associated hyperglycemia, individualized control objectives, management during clinical hospitalization (preadmission preparation, blood glucose management during hospitalization, insulin therapy, intensive care unit and non-intensive care unit management, ketoacidosis and hyperosmolar hyperglycemia, hypoglycemia treatment, perioperative blood glucose management, blood glucose management during enteral/parenteral nutrition, pregnancy with hyperglycemia or diabetes management, glucocorticoid application management, hospice care, transition from inpatient to outpatient, medication precautions, predischage treatment, etc.), the impact of a variety of hypoglycemic drugs on malignant tumors, the impact of tumor therapeutic drugs on blood glucose and outpatient management, including the establishment of archives of patients with malignant tumors, health examination of blood glucose and complications, long-term follow-up and evaluation. In addition, combined with the actual medical situation in China, the guidelines provide two-way referral and graded diagnosis and treatment for patients with tumor-associated hyperglycemia and put forward relevant suggestions and standards to facilitate the convenient implementation of medical institutions and medical personnel at all levels. The guidelines put forward the corresponding classification of recommendations according to the principle of evidence-based medical evidence classification, which will help clinicians to rationalize and standardize the management of patients with tumor-associated hyperglycemia, so as to improve their clinical outcome and prognosis. Here, we made an interpretation of the contents and recommendations.

[Key words] Tumor-associated hyperglycemia; Management; Interpretation of guidelines

近年来, 非传染性疾病是造成全球人类死亡的主要原因, 而癌症已成为目前世界各国人类死亡的主要原因, 也是提高预期寿命最重要的障碍。最新的全球恶性肿瘤统计数据显示,

2020年全球新发恶性肿瘤病例1 929万例, 全球恶性肿瘤死亡病例996万例, 其中中国新发恶性肿瘤457万人, 占全球新发病人数的23.7%, 死亡人数300万, 占死亡总人数的30%, 均远超其他

国家^[1]。

糖尿病是以胰岛素分泌障碍和（或）胰岛素作用失常而导致高血糖为特征的一组代谢性疾病，根据世界卫生组织（World Health Organization, WHO）诊断标准，2017年患病率已升至11.2%，中国已成为世界第一的糖尿病大国^[2]。指南第一部分指出，中国恶性肿瘤和糖尿病发病率呈逐年上升趋势，恶性肿瘤与糖尿病关系密切^[3]。流行病学研究发现，糖尿病患者罹患多种恶性肿瘤的风险显著增加^[4]。糖尿病与日益加重的恶性肿瘤负担并存，引起了很多专家对糖尿病与恶性肿瘤之间的流行病学和生物学关系的兴趣^[5]。同时指南指出，肿瘤患者中血糖升高很常见，肿瘤本身的代谢紊乱，肿瘤治疗过程中涉及到的化疗药物、糖皮质激素、靶向药物和免疫检查点抑制剂，以及治疗肿瘤所使用的辐射和手术，均有可能导致高血糖，肿瘤患者本身也可以合并高血糖或糖尿病^[3]。这些情况所导致的血糖升高，往往情况比较复杂，很多时候血糖波动较大且难以控制，临床上管理难度较大；更重要的是，有研究^[6]显示，无论是哪种情况所致的高血糖，其血糖控制情况的好坏与肿瘤患病风险和不良预后均密切相关。因此，如何管理好肿瘤患者的血糖是决定肿瘤防治以及预后的重要指标之一，也是本次制定《肿瘤相关性高血糖管理指南（2021年版）》最重要的动机。本次指南主要对肿瘤相关性高血糖的概念和诊断、住院期间的管理、降糖和抗肿瘤药物对血糖的影响、长期门诊随访管理和双向转诊等予以关注和阐述^[3]，本文将就以上几个方面对指南进行解读。

1 肿瘤相关性高血糖的概念与诊断

事实上，无论是患者自身还是临床医务人员，都很容易忽视肿瘤患者的血糖管理问题。与普通糖尿病患者类似，肿瘤患者的高血糖也需要个性化的管理，并强调医护共同参与，这也是本指南多次强调的基本观点。

在本指南中特别提出了肿瘤相关性高血糖的概念，即由肿瘤本身或肿瘤治疗过程中导致的高血糖以及肿瘤患者合并已知的糖尿病状态，即空腹血

糖 >6.1 mmol/L，随机血糖水平 >7.8 mmol/L。肿瘤相关性糖尿病是指典型的糖尿病症状（三多一少症状）合并随机静脉血浆葡萄糖 ≥ 11.1 mmol/L或FPG ≥ 7.0 mmol/L或口服葡萄糖耐量试验（oral glucose tolerance test, OGTT）的2 h静脉血浆葡萄糖 ≥ 11.1 mmol/L。无典型症状者，需隔天复查确认。诊断的前提是在肿瘤患者人群中，且很多情况下是在肿瘤的治疗过程中，既往无糖尿病史的肿瘤患者，若HbA1c $\geq 6.5\%$ ，提示已可能为新发的肿瘤相关性糖尿病^[3]。以上标准在诊断上仍然需要排除其他原因引起的血糖升高，如高糖饮食、药物损伤、肝功能异常、胰腺损伤等。

2 肿瘤相关性高血糖患者住院期间的诊治意见解读

在肿瘤患者住院期间，本指南在多处强调应由专业的团队进行血糖管理，因为大量的研究证明，专业的团队对血糖的管理可以缩短住院时间，有助于血糖控制，改善预后^[7-9]。且有研究^[10-11]表明，即使专家并未实地查看患者，仅通过电子病历审查并提出相关建议也可使血糖和低血糖的发生率降低30%~40%。在肿瘤患者的血糖控制目标方面，本指南仍然借鉴沿用普通糖尿病患者血糖控制目标分层，并根据具体的肿瘤患者院内外血糖值和内外科诊断、治疗情况制定个性化的血糖控制目标，以满足每例患者的需求和偏好，综合平衡治疗风险和益处，从而优化患者参与度和自我管理效能^[12]，这体现了对肿瘤患者血糖进行个体化和医患共同参与管理的特点。肿瘤相关性高血糖的评估可通过HbA1c、糖化白蛋白、持续血糖监测（continuous glucose monitoring, CGM）和自我血糖监测（self monitoring of blood glucose, SMBG）来进行。同时，针对近年来最新的血糖监测技术的发展更新，本指南对CGM技术在临床应用方面，也及时推荐了葡萄糖目标范围内时间（time in range, TIR）作为新的评价血糖控制的重要指标之一^[13-15]。TIR控制目标70%与HbA1c控制目标7%相对应，葡萄糖低于目标范围时间（time below range, TBR）（糖尿病患者血糖水平 <3.9 mmol/L，非糖尿病患者血糖水

平 <3.0 mmol/L)和高于目标范围时间(time above range, TAR)(血糖水平 >10.0 mmol/L)是重新调整治疗方案的依据^[16-18]。对于很多肿瘤患者而言,实时和扫描式的CGM结合每天多次注射、持续皮下胰岛素输注和其他形式的胰岛素治疗可有效地降低HbA1c水平和血糖,可取代SMBG。当然,这一切的基础是良好的关于血糖监测的技术培训和教育^[19-21]。在住院医嘱上,本指南同时也推荐使用计算机化的医嘱输入,这能防止药物相关性错误,提高药物管理的效率,并可以改善平均血糖水平而不增加低血糖的发生率^[22-24]。这些都是本指南基于最新的血糖监测方面的研究成果结合临床实践进行的推荐,具有重要的现实意义和实用价值。

对于肿瘤相关性高血糖患者住院期间的低血糖管理也是非常重要的,本指南提出:1级低血糖是指血糖浓度为 $3.0\sim 3.9$ mmol/L;2级低血糖是指血糖浓度 <3.0 mmol/L,通常导致低血糖的中枢神经系统症状;3级低血糖是已出现以精神和(或)身体功能改变为特征的临床事件,需要对症治疗才能康复。2、3级低血糖需要立即纠正血糖^[25]。对于有糖尿病史的肿瘤患者,既往3个月内如未进行HbA1c检测,则需进行HbA1c检测;有糖尿病史的患者还应询问既往有无低血糖事件,判断低血糖的发生风险和程度。医院应预先制定好低血糖防范方案,为每例患者制定预防和低血糖的计划。同时,应借助最新的人工智能技术来提高血糖管理的效率,减少低血糖事件的发生。我们团队最新的研究^[26]显示,信息整合化全院血糖管理系统对肿瘤合并高血糖患者的血糖管理具有明显的优势,可改善患者血糖水平,减少高风险血糖事件的发生,缩短平均住院日,提升患者治疗质量,这与本指南的推荐相吻合,后期随着国家政策的推进,主动健康模式下的人工智能可穿戴设备的广泛应用将在多个慢病领域大显身手,在肿瘤相关性高血糖方面的应用和管理也将是热点之一,这点也将在我们后面指南的更新中得到体现。

胰岛素治疗是很多住院肿瘤相关性高血糖患者普遍接受的一种疗法,对于危重患者而言,本指南推荐制定个性化的血糖控制目标,通过持续

静脉胰岛素输注并根据血糖波动和胰岛素剂量调整是实现血糖目标的最有效方法^[27]。在重症监护病房外,基础胰岛素或基础+餐时方案是非危重病住院患者口服降糖药物控制不佳或限制口服降糖药物的首选治疗方案。与很多普通糖尿病患者的推荐方案不同,对于营养摄入良好的肿瘤患者,预混胰岛素方案推荐首选,这点根据患者的依从性来作出选择。同时,本指南认为对于接受每天多次注射胰岛素的肿瘤患者,在能够安全管理胰岛素泵的前提下应考虑使用胰岛素泵治疗,尤其对于老年患者,胰岛素泵持续皮下胰岛素输注是值得推荐和提倡的方式^[12, 25]。餐时可以通过短效或速效胰岛素提供胰岛素的量,根据食量的大小调整胰岛素剂量,不进食正在接受持续的肠内或肠外营养的肿瘤患者,可每4~6 h注射1次,根据血糖监测情况调整胰岛素剂量^[28-29]。由于低血糖发生率较高,预混胰岛素方案在住院期间的使用不常规推荐^[30-31]。同时,指南也不鼓励患者在住院期间总是根据检测血糖的结果临时来决定胰岛素注射剂量,而是需要根据患者病情将胰岛素的使用剂量进行长期的规划,一方面有利于患者的依从性,保持大致恒定的胰岛素注射剂量,另一方面,这也便于为患者后期康复出院做准备。

由于相关循证医学证据在肿瘤相关性高血糖患者中的缺乏,针对肿瘤相关性高血糖患者的一些特殊情况,本指南中关于住院期间患者的血糖管理措施,包括酮症酸中毒和高渗性高血糖状态,围手术期血糖管理,非进食肠内或肠外营养情况下血糖的管理,妊娠合并高血糖或糖尿病的管理主要根据专家组的推荐意见^[12]。住院期间,需要对患者进行全面的系统化的评估,具体包括:①确定糖尿病或高血糖的诊断,并回顾患者既往的血糖控制情况和可能的危险因素;②评估糖尿病并发症和共病情况;③强调医护共同参与制定住院期间及后续的管理。针对肿瘤治疗过程中糖皮质激素的应用,国外通常推荐中效胰岛素作为标准方案,但由于中效胰岛素在中国各个医院已很少有使用,故本指南中仍列出了基础胰岛素+必要时使用餐时胰岛素或口服降糖药物进行控

制^[12, 32-34]。在肿瘤相关性高血糖患者的临终关怀方面, 血糖、血脂等指标的控制并非是最重要的, 必要时可以降低强度甚至停止这些方面的控制措施, 以提高肿瘤患者总体舒适度, 减轻痛苦, 维持生活质量和尊严^[36]。由住院向门诊和出院的过渡同样需要作好对肿瘤患者个性化的出院计划和院外培训^[37]。

3 药物对血糖的影响

目前的研究发现, 一些抗肿瘤药物会对血糖产生影响, 同时, 很多降糖药物也会对肿瘤产生影响。作为使用最广泛的抗糖尿病药物, 胰岛素在肿瘤患者中的使用备受争议。有学者在一些体外实验中发现, 胰岛素与肿瘤细胞的增殖及分化有一定的相关性^[38]; 在一些回顾性分析中也发现, 胰岛素尤其是甘精胰岛素的使用似乎与多种肿瘤的发生、发展有一定的联系^[39-40]。但同时也有大型的随机对照研究^[41-42]并未发现甘精胰岛素或地特胰岛素的使用与肿瘤发生、发展有关, 其大剂量的致癌性还需进一步探讨, 而德谷胰岛素在这方面尚缺乏相应的证据。也有研究^[43-45]发现, 部分磺脲类降糖药的使用与恶性肿瘤相关的死亡率及患癌风险增加密切相关, 但缺乏进一步的严格的随机对照试验和基础研究证据。二甲双胍作为广泛用于2型糖尿病的一线药物, 大量的临床研究均证实其具有一定抗肿瘤作用, 尤其是在乳腺癌领域^[46], 基础研究证明其主要机制是通过AMP活化蛋白激酶(AMP-activated protein kinase, AMPK)依赖性和非依赖性途径多靶点抑制肿瘤细胞的增殖和分化^[47-50]。但有专家指出, 部分研究存在多种偏倚, 有可能导致结果夸大其词, 二甲双胍对癌细胞的直接抑制作用还缺乏大规模随机对照的前瞻性临床研究数据的支持^[51]。有研究^[52-53]发现, 噻唑烷二酮类药物的使用可抑制部分肿瘤细胞的生长, 但也有研究^[54]发现, 吡格列酮的使用似乎与膀胱癌的发生有一定的联系, 但该研究随后的结果又显示这种趋势随着时间的推移消失。而罗格列酮在这方面的研究比较少且时间较短, 评价其安全性尚待时日^[55]。肠促胰素类似物和DPP-4抑制剂对于肿瘤的影响也是众说纷纭。有研究^[56]发现,

胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)似乎与胰腺癌的发生有关, 而在临床研究中并未能重现该结果, 同时GLP-1可促进降钙素的释放, 增加患甲状腺髓样癌的风险, 但大规模临床研究发现, 对于其他类型的甲状腺癌, GLP-1的使用是安全的, 因此, GLP-1主要禁用于胰腺癌和甲状腺髓样癌。而对于DPP-4抑制剂来说, 有研究^[57-59]发现, 其促进部分肿瘤的发生、发展, 而在另一些研究^[60]中, DPP-4抑制剂不仅与肿瘤发生率无关, 甚至增加化疗的敏感性, 还有研究^[61]认为, DPP-4抑制剂对于肿瘤主要是促进其侵袭和转移, 与发生、发展无关。因此, DPP-4抑制剂对肿瘤的影响较为复杂, 需要进一步的临床和基础研究。对于钠-葡萄糖共转运子2(sodium-glucose cotransporter 2, SGLT2)抑制剂而言, 目前有少量研究^[62-63]发现, SGLT2抑制剂的使用与部分恶性肿瘤的发病率升高有相关性, 但也有研究^[64-66]指出, 使用SGLT2抑制剂与未使用SGLT2抑制剂相比并未增加恶性肿瘤的发生率, 甚至有抗癌作用, 因此, 其安全性尚需进一步大规模随机对照临床研究证实。

在肿瘤治疗过程中, 部分药物和技术手段也可能引起血糖的升高, 导致暂时性或永久性的高血糖或糖尿病。药物包括化疗过程中所使用的糖皮质激素、铂类药物、5-氟尿嘧啶和L-天冬氨酸酶, 靶向药物中mTOR抑制剂(依维莫司等)和酪氨酸激酶抑制剂(尼洛替尼等)和免疫检查点抑制剂中的程序性死亡[蛋白]-1(programmed death-1, PD-1)/程序性死亡[蛋白]配体-1(programmed death ligand-1, PD-L1)抑制剂(伊匹单抗或派姆单抗等)以及部分内分泌治疗药物, 其机制可能与直接破坏胰岛β细胞, 抑制胰岛素的合成和降低胰岛素分泌及加重胰岛素抵抗有关^[67-71]。有研究^[72-73]显示, 放疗也可以导致血糖升高, 其分子机制不明。关于这方面的基础和临床研究证据也在不断增加, 如对于mTOR抑制剂所诱导的高血糖, 有专家建议: 在开始治疗前应监测空腹血糖及糖化血红蛋白, 治疗后第1个月应每两周检测1次空腹血糖, 之后每个月检查1次, 同时每3个月检测1次糖化血红蛋白, 一旦

血糖水平 >13.9 mmol/L, 则应迅速请内分泌科医师会诊^[74]; 此外, 还有专家针对应用胰岛素抵抗相关或阻断胰岛素受体的抗癌药物的患者之高血糖提出了一些管理方案^[75], 期望在下一版指南的更新中得到体现。同时, 有很多基础研究认为, 自噬与糖酵解及肿瘤密切, 是否可以通过自噬的调控和糖酵解的调节实现对肿瘤细胞生命周期的管控也是一个值得探讨的话题。在实际的临床应用中, 对于有合并糖尿病和存在糖尿病高危因素的肿瘤患者来说, 应用药物前后监测血糖, 有利于早期发现血糖紊乱, 同时增加对生活方式的改善力度, 提前实施干预, 为患者带来更好的预后。

4 肿瘤相关性高血糖的长期门诊随访管理和双向转诊意见解读

对于糖尿病患者而言, 患肿瘤的概率显著上升, 因此, 早期接受肿瘤的筛查和随访管理, 对于糖尿病患者来说可以降低患癌风险^[76-77]; 而对于肿瘤患者来说, 若合并糖尿病或高血糖, 也会导致不良预后, 仅在住院期间控制好血糖是远远不够的, 长期的门诊随访且管理好血糖、糖尿病对于肿瘤患者来说意义重大, 可以延长预期寿命并改善生活质量^[78-79]。因此, 本指南也为肿瘤患者提出了个性化的门诊和长期随访管理的推荐意见。

与普通糖尿病和高血糖患者不同, 门诊的肿瘤患者应根据肿瘤病情变化和治疗进展制定相应的目标和管理方案。本指南认为需要根据患者的具体情况制定针对性的长期的门诊血糖控制目标和定期随访内容, 包括持续且规律的血糖自我监测结果, 患者一般情况, 用药及不良反应情况, 以及针对高血糖患者的辅助检查和生化指标如肝肾功能、血糖、血脂、糖化血红蛋白、尿蛋白, 眼底筛查, 踝肱指数和血管彩超, 心电图和心脏超声, 神经传导速率等。并根据肿瘤患者的个体情况, 在不同时期随访不同的内容。基于互联网的远程管理对肿瘤相关性高血糖的控制可能增强患者的依从性, 提高诊疗效率, 值得进一步推广和应用。

分级诊疗是中国的基本医疗保障制度之一, 肿瘤高血糖患者出现多种情况, 如病因和分型不

能明确、儿童或青少年糖尿病患者、妊娠和哺乳期血糖异常者、血糖长期控制不达标者、出现严重的糖尿病急性并发症和慢性并发症或合并症者, 需要转上级医院; 而在诊断明确、并发症和合并症病情控制稳定、长期的诊疗方案明确后, 则需要转回基层医疗卫生机构。在分级诊疗双向转诊方面, 由于缺乏针对中国肿瘤患者血糖管理分级诊疗和双向转诊方面相关的临床研究证据, 专家组主要参考《中国2型糖尿病防治指南(2020年版)》、《2型糖尿病分级诊疗与质量管理专家共识》和《基层糖尿病微血管病变筛查与防治专家共识》等相关的共识和指南^[80-82], 很多推荐的意见均为专家个人和集体讨论的经验总结, 相信随着对中国肿瘤患者血糖长期管理和随访的研究结果揭晓, 指南会根据最新的更高等级的循证医学证据作出相应的更新。

5 总结与展望

近年来国际和国内学术界对肿瘤相关性高血糖和肿瘤患者血糖管理方面的认识和了解仍处于不断完善的过程中。对于本指南的观点, 临床医师应在广泛参考的基础上保持谨慎的态度, 避免盲从, 中国抗癌协会肿瘤内分泌专委会和重庆市中西医结合学会肿瘤内分泌分会也会定期组织专家组对指南进行更新。同时希望中国学者能在后期积极开展针对肿瘤患者血糖管理的临床和基础研究, 共同推动肿瘤患者血糖管理标准化诊疗体系的建立, 为中国肿瘤患者谋求更大的福祉。

[参 考 文 献]

- [1] FERLAY J, COLOMBET M, SOERJOMATARAM I, et al. Cancer statistics for the year 2020: an overview [J]. *Int J Cancer*, 2021. [Online ahead of print]
- [2] LI Y Z, TENG D, SHI X G, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study [J]. *BMJ*, 2020, 369: m997.
- [3] 中国抗癌协会肿瘤内分泌专业委员会, 重庆市中西医结合学会肿瘤内分泌分会. 肿瘤相关性高血糖管理指南(2021年版) [J]. *中国癌症杂志*, 2021, 31(7): 651-688. Onco-endocrinology Society of China Anti-Cancer Association, Onco-endocrinology Committee of Chongqing Association of Integrative Medicine. Guidelines for the management of tumor-associated hyperglycemia (2021 edition) [J]. *China Oncol*, 2021, 31(7): 651-688.

- [4] GIOVANNUCCI E, HARLAN D M, ARCHER M C, et al. Diabetes and cancer: a consensus report [J] . *CA Cancer J Clin*, 2010, 60(4): 207–221.
- [5] OHKUMA T, PETERS S A E, WOODWARD M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events [J] . *Diabetologia*, 2018, 61(10): 2140–2154.
- [6] GIRI B, DEY S, DAS T, et al. Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: an update on glucose toxicity [J] . *Biomedecine Pharmacother*, 2018, 107: 306–328.
- [7] GARG R, SCHUMAN B, BADER A, et al. Effect of preoperative diabetes management on glycemic control and clinical outcomes after elective surgery [J] . *Ann Surg*, 2018, 267(5): 858–862.
- [8] WANG Y J, SEGELKE S, HAWKINS R M, et al. Impact of glucose management team on outcomes of hospitalization in patients with type 2 diabetes admitted to the medical service [J] . *Endocr Pract*, 2016, 22(12): 1401–1405.
- [9] BANSAL V, MOTTALIB A, PAWAR T K, et al. Inpatient diabetes management by specialized diabetes team versus primary service team in non-critical care units: impact on 30-day readmission rate and hospital cost [J] . *BMJ Open Diabetes Res Care*, 2018, 6(1): e000460.
- [10] RUSHAKOFF R J, SULLIVAN M M, MACMASTER H W, et al. Association between a virtual glucose management service and glycemic control in hospitalized adult patients: an observational study [J] . *Ann Intern Med*, 2017, 166(9): 621–627.
- [11] ARNOLD P, SCHEURER D, DAKE A W, et al. Hospital guidelines for diabetes management and the joint commission-American Diabetes Association inpatient diabetes certification [J] . *Am J Med Sci*, 2016, 351(4): 333–341.
- [12] BUSE J B, WEXLER D J, TSAPAS A, et al. Erratum. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [J] . *Diabetes Care* 2020; 43: 487–493.
- [13] VIGERSKY R A, MCMAHON C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes [J] . *Diabetes Technol Ther*, 2019, 21(2): 81–85.
- [14] KRÖGER J, REICHEL A, SIEGMUND T, et al. Clinical recommendations for the use of the ambulatory glucose profile in diabetes care [J] . *J Diabetes Sci Technol*, 2020, 14(3): 586–594.
- [15] LIVINGSTONE R, BOYLE J G, PETRIE J R. How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes? [J] . *Diabet Med*, 2020, 37(4): 513–521.
- [16] MESSER L H, BERGET C, VIGERS T, et al. Real world hybrid closed-loop discontinuation: predictors and perceptions of youth discontinuing the 670G system in the first 6 months [J] . *Pediatr Diabetes*, 2020, 21(2): 319–327.
- [17] ADLER A I, STRATTON I M, NEIL H A, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study [J] . *BMJ*, 2000, 321(7258): 412–419.
- [18] DUCKWORTH W, ABRAIRA C, MORITZ T, et al. Glucose control and vascular complications in veterans with type 2 diabetes [J] . *N Engl J Med*, 2009, 360(2): 129–139.
- [19] GARG R, SCHUMAN B, BADER A, et al. Effect of preoperative diabetes management on glycemic control and clinical outcomes after elective surgery [J] . *Ann Surg*, 2018, 267(5): 858–862.
- [20] VAN DEN BOOM W, SCHROEDER R A, MANNING M W, et al. Effect of A1C and glucose on postoperative mortality in noncardiac and cardiac surgeries [J] . *Diabetes Care*, 2018, 41(4): 782–788.
- [21] SETJI T, HOPKINS T J, JIMENEZ M, et al. Rationalization, development, and implementation of a preoperative diabetes optimization program designed to improve perioperative outcomes and reduce cost [J] . *Diabetes Spectr*, 2017, 30(3): 217–223.
- [22] GILLAZEAU F, CHAN E, TRINQUART L, et al. Computerized advice on drug dosage to improve prescribing practice [J] . *Cochrane Database Syst Rev*, 2013(11): CD002894.
- [23] WEXLER D J, SHRADER P, BURNS S M, et al. Effectiveness of a computerized insulin order template in general medical inpatients with type 2 diabetes: a cluster randomized trial [J] . *Diabetes Care*, 2010, 33(10): 2181–2183.
- [24] SCHNIPPER J L, LIANG C L, NDUMELE C D, et al. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial [J] . *Endocr Pract*, 2010, 16(2): 209–218.
- [25] AGIOSTRATIDOU G, ANHALT H, BALL D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, the Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D exchange [J] . *Diabetes Care*, 2017, 40(12): 1622–1630.
- [26] JIANG J, PU D L, HU R Z, et al. Evaluation of the efficacy of the hospital glycemic management system for patients with malignant tumors and hyperglycemia [J] . *Diabetes Metab Syndr Obes*, 2021, 14: 2717–2725.
- [27] DRAZNIN B, GILDEN J, GOLDEN S H, et al. Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action [J] . *Diabetes Care*, 2013, 36(7): 1807–1814.
- [28] COLUNGA-LOZANO L E, GONZALEZ TORRES F J, DELGADO-FIGUEROA N, et al. Sliding scale insulin for non-critically ill hospitalized adults with diabetes mellitus [J] . *Cochrane Database Syst Rev*, 2018, 11(11): CD011296.
- [29] GIUGLIANO D, CHIODINI P, MAIORINO M I, et al. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and

- meta-analysis of randomized controlled trials [J] . *Endocrine*, 2016, 51(3): 417-428.
- [30] BELLIDO V, SUAREZ L, RODRIGUEZ M G, et al. Comparison of basal-bolus and premixed insulin regimens in hospitalized patients with type 2 diabetes [J] . *Diabetes Care*, 2015, 38(12): 2211-2216.
- [31] IYENGAR R, FRANZESE J, GIANCHANDANI R. Inpatient glycemic management in the setting of renal insufficiency/failure/dialysis [J] . *Curr Diab Rep*, 2018, 18(10): 75.
- [32] KWON S, HERMAYER K L, HERMAYER K. Glucocorticoid-induced hyperglycemia [J] . *Am J Med Sci*, 2013, 345(4): 274-277.
- [33] SEGELKE S A, GIBBS J, DRAZNIN B. Pilot study of using neutral protamine Hagedorn insulin to counteract the effect of methylprednisolone in hospitalized patients with diabetes [J] . *J Hosp Med*, 2011, 6(3): 175-176.
- [34] MAYNARD G, WESORICK D H, O'MALLEY C, et al. Subcutaneous insulin order sets and protocols: effective design and implementation strategies [J] . *J Hosp Med*, 2008, 3(5 Suppl): 29-41.
- [35] BRADY V, THOSANI S, ZHOU S H, et al. Safe and effective dosing of basal-bolus insulin in patients receiving high-dose steroids for hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy [J] . *Diabetes Technol Ther*, 2014, 16(12): 874-879.
- [36] SIMPSON F R, PAJEWSKI N M, NICKLAS B, et al. Impact of multidomain lifestyle intervention on frailty through the lens of deficit accumulation in adults with type 2 diabetes mellitus [J] . *J Gerontol A Biol Sci Med Sci*, 2020, 75(10): 1921-1927.
- [37] UMPIERREZ G E, REYES D, SMILEY D, et al. Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes [J] . *Diabetes Care*, 2014, 37(11): 2934-2939.
- [38] SCIACCA L, MOLI R L, VIGNERI R. Insulin analogs and cancer [J] . *Front Endocrin*, 2012, 3: 21.
- [39] TSENG C H. Human insulin therapy is associated with an increased risk of lung cancer: a population-based retrospective cohort study [J] . *Front Endocrinol (Lausanne)*, 2019, 10: 443.
- [40] MANNUCCI E, MONAMI M, BALZI D, et al. Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients [J] . *Diabetes Care*, 2010, 33(9): 1997-2003.
- [41] POCOCK S J, SMEETH L. Insulin glargine and malignancy: an unwarranted alarm [J] . *Lancet*, 2009, 374(9689): 511-513.
- [42] ZINMAN B. Newer insulin analogs: advances in basal insulin replacement [J] . *Diabetes Obes Metab*, 2013, 15(Suppl 1): 6-10.
- [43] MONAMI M, BALZI D, LAMANNA C, et al. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality [J] . *Diabetes Metab Res Rev*, 2007, 23(6): 479-484.
- [44] MONAMI M, LAMANNA C, BALZI D, et al. Sulphonylureas and cancer: a case-control study [J] . *Acta Diabetol*, 2009, 46(4): 279-284.
- [45] HENDRIKS A M, SCHRIJNDERS D, KLEEFSTRA N, et al. Sulphonylurea derivatives and cancer, friend or foe? [J] . *Eur J Pharmacol*, 2019, 861: 172598.
- [46] LENG W L, JIANG J, CHEN B, et al. Metformin and malignant tumors: not over the hill [J] . *Diabetes Metab Syndr Obes: Targets Ther*, 2021, 14: 3673-3689.
- [47] MERRY B J. Molecular mechanisms linking calorie restriction and longevity [J] . *Int J Biochem Cell Biol*, 2002, 34(11): 1340-1354.
- [48] STEVENS R J, ALI R, BANKHEAD C R, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials [J] . *Diabetologia*, 2012, 55(10): 2593-2603.
- [49] LI Y, XU S Q, MIHAYLOVA M M, et al. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice [J] . *Cell Metab*, 2011, 13(4): 376-388.
- [50] KISFALVI K, EIBL G, SINNETT-SMITH J, et al. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth [J] . *Cancer Res*, 2009, 69(16): 6539-6545.
- [51] SUISSA S, AZOULAY L. Metformin and cancer: mounting evidence against an association [J] . *Diabetes Care*, 2014, 37(7): 1786-1788.
- [52] LUCONI M, MANGONI M, GELMINI S, et al. Rosiglitazone impairs proliferation of human adrenocortical cancer: preclinical study in a xenograft mouse model [J] . *Endocr Relat Cancer*, 2010, 17(1): 169-177.
- [53] NAGAMINE M, OKUMURA T, TANNO S, et al. PPAR gamma ligand-induced apoptosis through a p53-dependent mechanism in human gastric cancer cells [J] . *Cancer Sci*, 2003, 94(4): 338-343.
- [54] BOSETTI C, ROSATO V, BUNIATO D, et al. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis [J] . *Oncologist*, 2013, 18(2): 148-156.
- [55] KURISHIMA K, WATANABE H, ISHIKAWA H, et al. Survival of patients with lung cancer and diabetes mellitus [J] . *Mol Clin Oncol*, 2017, 6(6): 907-910.
- [56] ELASHOFF M, MATVEYENKO A V, GIER B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies [J] . *Gastroenterology*, 2011, 141(1): 150-156.
- [57] SHI S, SRIVASTAVA S P, KANASAKI M, et al. Interactions of DPP-4 and integrin β 1 influences endothelial-to-mesenchymal transition [J] . *Kidney Int*, 2015, 88(3): 479-489.
- [58] SRIVASTAVA S P, GOODWIN J E, KANASAKI K, et al. Inhibition of angiotensin-converting enzyme ameliorates renal fibrosis by mitigating DPP-4 level and restoring antifibrotic microRNAs [J] . *Genes (Basel)*, 2020, 11(2): E211.
- [59] NAGEL A K, AHMED-SARWAR N, WERNER P M, et

- al. Dipeptidyl peptidase-4 inhibitor-associated pancreatic carcinoma: a review of the FAERS database [J] . *Ann Pharmacother*, 2016, 50(1): 27-31.
- [60] YANG F, TAKAGAKI Y, YOSHITOMI Y, et al. Inhibition of dipeptidyl peptidase-4 accelerates epithelial-mesenchymal transition and breast cancer metastasis via the *cxcl12/excr4/mTOR* axis [J] . *Cancer Res*, 2019, 79, 735-746.
- [61] WANG H, LIU X, LONG M, et al. NRF2 activation by antioxidant antidiabetic agents accelerates tumor metastasis [J] . *Sci Transl Med*, 2016, 8(334): 334ra51.
- [62] LIN H W, TSENG C H. A review on the relationship between SGLT2 inhibitors and cancer [J] . *Int J Endocrinol*, 2014, 2014: 719578.
- [63] TAUB M E, LUDWIG-SCHWELLINGER E, ISHIGURO N, et al. Sex-, species-, and tissue-specific metabolism of empagliflozin in male mouse kidney forms an unstable hemiacetal metabolite (M466/2) that degrades to 4-hydroxycrotonaldehyde, a reactive and cytotoxic species [J] . *Chem Res Toxicol*, 2015, 28(1): 103-115.
- [64] WU J H, FOOTE C, BLOMSTER J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis [J] . *Lancet Diabetes Endocrinol*, 2016, 4(5): 411-419.
- [65] SCAFOGLIO C, HIRAYAMA B A, KEPE V, et al. Functional expression of sodium-glucose transporters in cancer [J] . *Proc Natl Acad Sci*, 2015, 112(30): E4111-4119.
- [66] CHAO E C, HENRY R R. SGLT2 inhibition: a novel strategy for diabetes treatment [J] . *Nat Rev Drug Discov*, 2010, 9(7): 551-559.
- [67] VERGÈS B, CARIOU B. mTOR inhibitors and diabetes [J] . *Diabetes Res Clin Pract*, 2015, 110(2): 101-108.
- [68] VERGÈS B, WALTER T, CARIOU B. Endocrine side effects of anti-cancer drugs: effects of anti-cancer targeted therapies on lipid and glucose metabolism [J] . *Eur J Endocrinol*, 2014, 170(2): R43-R55.
- [69] GEUNA E, RODA D, RAFI S, et al. Complications of hyperglycaemia with PI3K-AKT-mTOR inhibitors in patients with advanced solid tumours on phase I clinical trials [J] . *Br J Cancer*, 2015, 113(11): 1541-1547.
- [70] FENG J P, YUAN X L, LI M, et al. Secondary diabetes associated with 5-fluorouracil-based chemotherapy regimens in non-diabetic patients with colorectal cancer: results from a single-centre cohort study [J] . *Colorectal Dis*, 2013, 15(1): 27-33.
- [71] SAĞLAM H S, KÖSE O, KUMSAR S, et al. Fasting blood glucose and lipid profile alterations following twelve-month androgen deprivation therapy in men with prostate cancer [J] . *Sci World J*, 2012, 2012: 696329.
- [72] NGUYEN N P, VOS P, VINH-HUNG V, et al. Altered glucose metabolism during chemoradiation for head and neck cancer [J] . *Anticancer Res*, 2009, 29(11): 4683-4687.
- [73] MEACHAM L R, SKLAR C A, LI S W, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study [J] . *Arch Intern Med*, 2009, 169(15): 1381-1388.
- [74] YIM C, MANSELL K, HUSSEIN N, et al. Current cancer therapies and their influence on glucose control [J] . *World J Diabetes*, 2021, 12(7): 1010-1025.
- [75] GOLDMAN J W, MENDENHALL M A, RETTINGER S R. Hyperglycemia associated with targeted oncologic treatment: mechanisms and management [J] . *Oncologist*, 2016, 21(11): 1326-1336.
- [76] SACERDOTE C, RICCERI F. Epidemiological dimensions of the association between type 2 diabetes and cancer: a review of observational studies [J] . *Diabetes Res Clin Pract*, 2018, 143: 369-377.
- [77] GBD CAUSES OF DEATH COLLABORATORS. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017 [J] . *Lancet*, 2018, 392(10159): 1736-1788.
- [78] FLORY J, FAROOKI A. Diabetes management in cancer patients [J] . *Oncology (Williston Park)*, 2016, 30(6): 565-570.
- [79] GILLIES R J, PILOT C, MARUNAKA Y, et al. Targeting acidity in cancer and diabetes [J] . *Biochim Biophys Acta Rev Cancer*, 2019, 1871(2): 273-280.
- [80] 阎德文, 肖新华. 2型糖尿病分级诊疗与质量管理专家共识 [J] . *中国医学前沿杂志(电子版)*, 2020, 12(5): 38-53.
YAN D W, XIAO X H. Experts consensus on the grading medical care and quality management of type 2 diabetes mellitus [J] . *Chin J Front Med Sci (Electron Version)*, 2020, 12(5): 38-53.
- [81] 中华医学会糖尿病学分会. 中国2型糖尿病防治指南(2020年版) [J] . *中华糖尿病杂志*, 2021, 13(4): 315-409.
Chinese Diabetes Society. Guidelines for the prevention and control of type 2 diabetes in China (2020 edition) [J] . *Chin J Diabetes*, 2021, 13(4): 315-409.
- [82] 中国微循环学会糖尿病与微循环专业委员会, 中国医疗保健国际交流促进会基层卫生分会基层糖尿病学部, 江苏省基层内分泌特色科室孵化联盟. 基层糖尿病微血管病变筛查与防治专家共识(2021年版) [J] . *中国医学前沿杂志(电子版)*, 2021, 13(6): 16-38.
Chinese Association of Diabetes and Microcirculation, Department of Primary Diabetes Care, Primary Health Branch of China International Exchange and Promotion Association for Medical and Healthcare, Jiangsu Incubation Federation for Specialized Endocrinology Department of Community Hospital. Expert consensus on screening and prevention of diabetic microangiopathy at the grass-roots level (2021 edition) [J] . *Chin J Front Med Sci (Electron Version)*, 2021, 13(6): 16-38.