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Research Progress of Metabolic Syndrome and Renal Cancer

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Abstract

Metabolic syndrome (MS) is a condition of metabolic abnormalities in genetically predisposed individuals that are caused by lifestyle habits such as consumption of diet rich in fat and lack of exercise. Few major symptoms include abnormal glucose tolerance, hypertension, abnormal lipid metabolism (including high triglycerides in the blood, low high density lipoprotein cholesterol, etc.), obesity, etc. Although metabolic syndrome has been found to be mainly related to cardiovascular diseases, diabetes, malignancy and other diseases, in recent years, more and more evidence has shown that MS is closely related to the occurrence, development and prognosis of kidney cancer, among which obesity and hypertension have been identified as major risk factors for kidney cancer. This article reviews the research progress on the relationship between MS and its components and the risk, invasiveness, and prognosis of renal carcinoma, so as to provide reference for the prevention, diagnosis, treatment and prognosis of renal cancer.

Key words metabolic syndrome, kidney cancer, risk, invasive, prognosis

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Introduction

Metabolic syndrome (MS) was first described by Reaven as "Syndrome X" [1]. MS refers to a cluster of metabolic abnormalities in genetically predisposed individuals due to lifestyle habits such as overeating or lack of exercise [2]. Metabolic syndrome is a series of clinical, biochemical and humoral metabolic disorders caused by insulin resistance, resulting in a variety of substance metabolic disorders syndrome, which has become a universal and serious health problem [3]. At present, MS has been found to be related to the occurrence and development of a variety of cancers, such as pancreatic cancer, gastric cancer, colorectal cancer, bladder cancer and so on [4-7]. Moreover, according to epidemiological studies, kidney cancer is associated with a variety of metabolic disorders, including obesity, hypertension, abnormal blood sugar, dyslipidemia and so on [8]. Renal cell carcinoma (RCC) is a common malignancy of the genitourinary system, accounting for 2%-3% of all adult malignancies. According to the recent data from the American Cancer Society, in the past year, approximately 62,720 new cases of kidney cancer were diagnosed in the United States, and 14, 240 deaths occured in the United States [9]. In Western countries, renal cellcarcinoma (RCC) accounts for 3% of adult malignancies, and the incidence of RCC is relatively low compared to other malignancies, but in recent years, the incidence and mortality rate have been increasing globally, especially in Asia due to changes in lifestyle and diet [10-13]. Obesity and high blood pressure in MS components are established risk factors for kidney cancer, and weight loss is a primary prevention measure recommended by the European Association of Urology (EAU) guidelines. The standard-of-care treatment for kidney cancer is partial or radical nephrectomy. However, due to the loss of functional renal parenchyma, the risk of chronic kidney disease (CKD) in patients with MS after radical surgery is significantly increased [14, 15]. There is still no consensus on how to identify and assess patients at high risk of CKD before surgery. Studying the relationship between MS and its components and kidney cancer can help clinicians to make decisions about kidney cancer prevention, treatment, follow-up, and prognosis.

Metabolic syndrome and renal cancer

MS, a combination of impaired glucose tolerance, obesity, hypertension, and dyslipidemia, is strongly associated with an increased risk of kidney cancer. A cohort study of 104, 274 Chinese men (including 131 new cases of kidney cancer) showed that compared with those without MS, people with MS had a higher risk of developing kidney cancer (HR = 1.97). Body weight (HR = 1.49), blood pressure (HR = 1.56) and blood lipid (HR = 1.77) were associated with the risk of renal cancer. The risk increases with the increase of the number of abnormal components in MS. This was also confirmed by a Turkish study, which not only showed a significant association between MS and kidney cancer (OR = 4.35, $P < 0.001$), but also increased the risk of kidney cancer from 4 to 6 times as the number of components increased from 3 to 5 [16]. Another retrospective study of 208 individuals f with kidney cancer combined with MS had a significant increase in more than three metabolic disorders compared with the control group. For the 4 components of MS: (1) There is a close relationship between diabetes and cancer. Epidemiological studies demonstrate a link between diabetes and kidney cancer where type 2 diabetes is independently associated with an increased risk in women [17]. Metformin, an anti-diabetic agent induces apoptosis and G0 / G1 phase cell cycle arrest, therebyinhibiting the growth of kidney cancer cells in vivo and in vitro [18]. (2) Number of clinical studies have shown that hypertension can increase the risk of kidney cancer. Colt et al. [19] found that hypertension can double the risk of kidney cancer. It is important to note that some interventions aimed at reducing high blood pressure such as diuretics and calcium channel blockers have been associated with papillary kidney cancer, but the reasons for this remains unclear [20]. (3) Evidence shows that obesity, as an independent risk factor, that is significantly associated with renal cancer [21, 22]. (4) In a prospective cohort study, Van Hemelrijck et al. [23] reported that glyceryl triester was the only lipid component statistically associated with renal cancer. In addition, statins used for the treatment of lipid diseases, especially hypercholesterolemia, have shown significant inhibitory effects on renal cancer cells in vitro, suggesting that abnormal lipid metabolism may be related to the growth, invasion, angiogenesis and metastasis of renal cancer cells [24]. **Figure 1** shows a research summary on metabolic syndrome and renal cancer.

Metabolic syndrome promotes development of kidney cancer

MS may be related to the pathogenesis of renal cancer, but little research has been conducted. Kocher et al. [25] found that in renal cancer cases with MS, hypertension is a single associated with tumor pathology. Patients with hypertension were more likely to have renal cancer with non-clear cell histology (OR = 1.42). Existing literature have shown that the Fuhrman grade in patients with renal cancer combined with MS is significantly higher than that in the group of pure renal cancer. A study of 668 patients with renal cancer found that the Fuhrman grade of patients with renal cancer combined with MS was significantly higher than that of the simple renal cancer group. Within the four MS groups including blood sugar, blood fat, body weight and blood pressure, only the first two are the risk factors with higher Fuhrman classification. Studies have shown that patients with renal clear cell carcinoma combined with MS not only have higher pathological stages and lower grades, but also possess larger tumor volume. Kocher et al. [25] found that although the combination of the four components of MS are associated with tumor grade and stage, if hypertension is included. Ozbek et al. [26] proposed that higher Fuhrman grade correlated with hypertension, diabetes and high triglyceride levels. Some recently published studies have shown that visceral adipose tissue appears to be a better indicator of obesity than BMI compared to subcutaneous adipose tissue. Zhu et al. [27] found that the percentage ratio of visceral adipose tissue is significantly associated with higher Fuhrman grade and may be an independent predictor of high-grade kidney cancer. However, visceral adipose tissue is likely to be protective against late-stage renal cancer patients receiving first-line targeted therapies such as sorafenib and sunitinib, and one retrospective study reported the fact that patients with higher levels of visceral fat had longer progression-free survival (PFS) and overall survival (OS) [28]. The conflicting effects of obesity on kidney cancer are detailed below. However, cohort studies have shown that patients with a high Furhman rating have a reduced risk of developing MS. Whether the combination or synergistic effect of each component of MS can explain the development and severity of kidney cancer remains unclear. The relationship between tumor grade and metabolism is expected to be confirmed by further large scale clinical studies.

Metabolic syndrome affects prognosis of renal carcinoma

A Finnish cohort study of 13,873 patients with kidney cancer showed that the risk of advanced kidney cancer at diagnosis was associated with hypertension (OR = 0.82) and lipid metabolism disorders (OR = 0.52) in MS patients. High blood pressure was associated with death in renal cancer patients (HR = 1.44), while other components of MS had no clear effect on the prognosis of renal cancer patients [29]. This supports hypertension as a

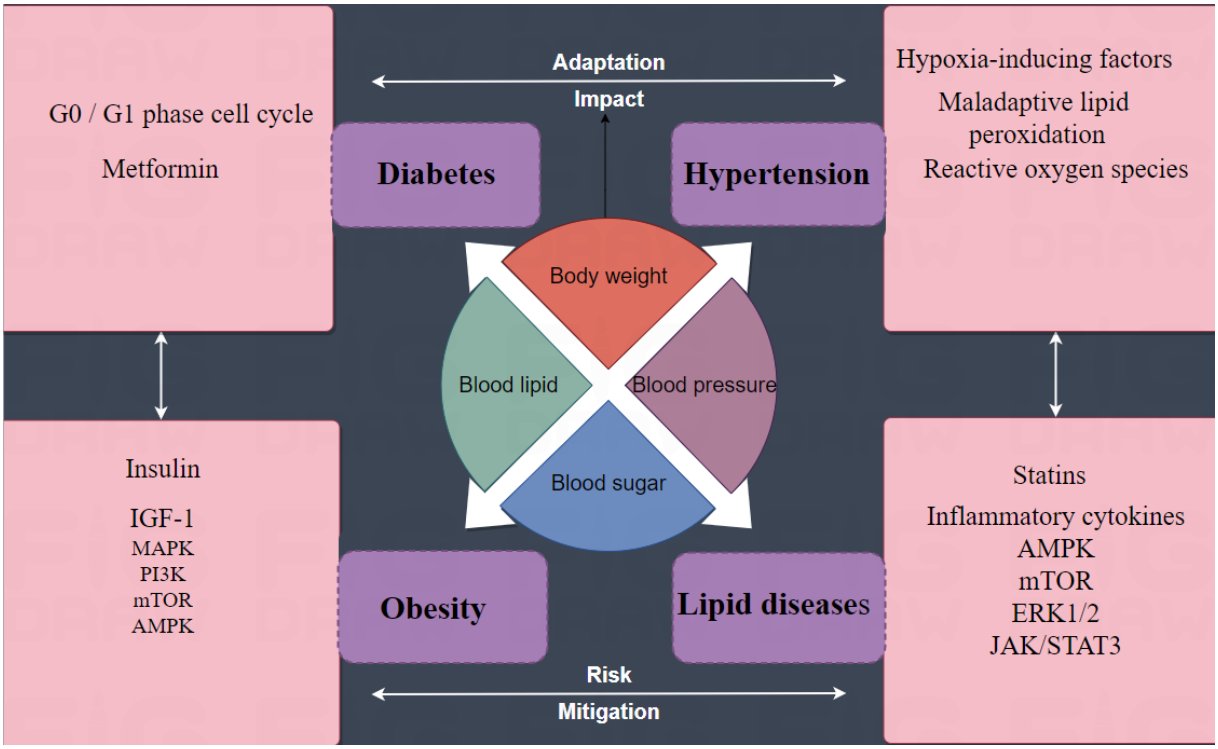

Figure 1. Metabolic syndrome and renal cancer. By inducing apoptosis and G0 / G1 phase cell cycle arrest, the antisugar metformin can inhibit the growth of kidney cancer cells in vivo and in vitro. Glyceryl triester was the only lipid component statistically associated with renal cancer. In addition, statins used for the treatment of lipid diseases, especially hypercholesterolemia, have shown significant inhibitory effects on renal cancer cells in vitro, suggesting that abnormal lipid metabolism may be related to the growth, invasion, angiogenesis and metastasis of renal cancer cells. Only one component of hypertension was associated with tumor pathology, patients with hypertension were more likely to have renal cancer with non-clear cell histology. Hyperinsulinemia/insulin resistance. The effect of insulin on cancer cell proliferation is thought to be related to IGF-1 stimulation. IGF-1 plays a role in promoting mitosis, cell migration, angiogenesis and inhibition of cytoplasmic death by activating mitogen-activated protein kinase (MAPK) and phosphoinositol 3 kinase (PI3K) signaling pathways. The combination of anti-IGF antibody and mammalian target of rapamycin (mTOR) inhibitor may be effective in renal cancer. Down-regulation of AMP-activated kinases and increased acetyl-CoA carboxylase are another common metabolic change that leads to increased fatty acid synthesis. Maladaptive lipid peroxidation and increased reactive oxygen species are thought to be pathogenic factors. In hypertensive states, upregulation of vasogenesis and hypoxia-inducing factors, including HIF-1α, is also thought to contribute to an increased risk of kidney cancer. The pro-inflammatory cytokines IL-6 and IL-10 are strongly expressed in both renal cancer cells and stroma, and IL-10 levels are higher in more advanced tumors (pT3). In vitro experiments have shown that adiponectin secreted by white adipose tissue can inhibit tumor growth by activating AMP-activated egg white kinase (AMPK) and regulate mTOR from below. Leptin can mediate the proliferation of kidney cancer AKI-2 cells by activating extracellular signal-regulated kinase (ERK1/2) and janus kinase/signal transduction and transcriptional activator 3 (JAK/STAT3) signaling pathways, and elevated serum leptin levels and leptin receptor overexpression are associated with renal cancer invasion and progression. AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR: mammalian target of rapamycin; ERK1/2: extracellular regulated protein kinases; JAK/STAT3: janus kinase/signal transduction and transcriptional activator 3; MAPK: mitogen-activated protein kinase; IGF-1: Insulin-like growth factor 1; PI3K: An intracellular phosphatidylinositol kinase that is related to the products of cancer genes such as V.SC and V.R.AS, and which itself has serine/threonine (Ser/Thr) kinase activity.

prognostic factor for renal cancer. Another study found that kidney cancer patients with MS had shorter PFS, but there was no relationship between PFS and other four components, suggesting the need to include MS rather than its components in the assessment of kidney cancer patients [30]. However, some studies have also shown that MS is an independent source of neoplastic idiogenesis (CSS) (P = 0.017) [31]. The inconsistent results of the above studies on MS and renal cancer prognosis may be related to the inclusion of different factors such as pathological type of renal cancer, lymph node metastasis, and patient weight. MS has a significant negative effect on perioperative and clinical recovery of renal carcinoma. Whether laparoscopy or open surgery, the operation time, intraoperative bleeding, postoperative intestinal function recovery time, postoperative movement time, postoperative fever, retroperitoneal drainage tube removal time, and postoperative hospital stay of renal cancer patients with MS

were different than those of non-MS patients. A recent study showed that in 25,875 patients with renal cancer who underwent partial nephrectomy (PN), MS and its components consistently and strongly predicted perioperative complications after PN, and the strength of the effect was positively proportional to the number of components, less than 3 components were filled [32]. The relationship between various components of MS and kidney cancer has been widely discussed and no consensus has been reached. Meta-analyses have shown that hyperglycemia is associated with poorer OS, CSS, and no recurrent time of survival (RFS) [33]. But other texts show that the relationship is insignificant [30, 34, 35]. Regarding hypertension and renal cancer outcomes, some studies have shown a negative impact of hypertension on CSS and overall mortality [36], while others have shown no significant consistency between the two [37]. There are few studies on the association between dyslipidemia and renal cancer, and studies have shown that elevated serum triglycerides (> 250mg/dL) are independently associated with poor PFS [30, 38]. The use of statins after surgery can improve the survival rate of patients with kidney cancer [39, 40]. It is worth mentioning that obesity is a recognized risk factor for kidney cancer, but the incidence of advanced kidney cancer is low in obese patients, that is, the so-called "fat paradox" [41, 42]. Studies have shown that high visceral adipose tissue is associated with improved renal cancer prognosis, especially after nephrectomy [41, 43]. One possible reason for this discrepancy is cachexia due to tumor depletion. On the other hand, it may be that some studies do not strictly distinguish between true morbid obesity and mild obesity. At the same time, obese patients visit hospitals relatively more often, which may help in early diagnosis of the disease [44]. In addition, MS can cause irreversible organoplasmic lesions of the kidney. Alexander et al. [14] found that compared with renal cancer patients without underlying disease, MS patients were more likely to have tubular atrophy, renal interstitial fibrosis, and arteriosclerosis, and that glomerular filtration rate (eGFR) was significantly lower in MS patients 1 year after nephrectomy. The study of Zhang et al. [15] showed that the eGFR level of MS patients was significantly lower than that of non-MS patients 2 years after radical surgery, and the CKD stage was more severe, and the recovery rate was significantly reduced. Studies have shown that MS can affect the compensation of healthy renal function after unilateral radical nephrectomy in patients with renal cancer. Renal dysfunction may be one of the ways MS directly affects the prognosis of patients with renal cancer [45].

Metabolic syndrome influences development mechanism of renal carcinoma

Various mechanisms have been proposed to untangle the link between MS and cancer progression. MS is associated with a variety of proven risk factors for cancer, such as age, physical inactivity, unhealthy diet and smoking, known as the "common soil hypothesis" [46, 47]. Currently, the strongest evidence for an association between MS and cancer centers on hyperinsulinemia/insulin resistance. The effect of insulin on cancer cell proliferation is thought to be related to IGF-1 stimulation [48, 49]. IGF-1 plays a role in promoting mitosis, cell migration, angiogenesis and inhibition of cytoplasmic death by activating mitogen-activated protein kinase (MAPK) and phosphoinositol 3 kinase (PI3K) signaling pathways [50, 51]. In vitro experiments indicate that the combination of anti-IGF antibody and mammalian target of rapamycin (mTOR) inhibitor may be effective in renal cancer [52]. MS may also influence kidney cancer through cell metabolism. For example, many metabolic abnormalities in patients with kidney cancer may be associated with VHL loss, which leads to pathologic changes including glycolysis and oxidative phosphorylation [53]. In addition, a Warburg-like shift dependent on anaerobic metabolism can be observed in kidney cancer [54]. Down-regulation of AMP-activated kinases and increased acetyl-CoA carboxylase are another common metabolic change that leads to increased fatty acid synthesis [55]. The change of metabolic pathway reduces the metabolic efficiency of normal cells, and the tumor cells make use of the excess substrate, and the metabolism is strong. This may be one of the mechanisms by which MS leads to the progression of kidney cancer. It also suggests that research and drug development targeting alternative sources of energy or fat production may be promising [56]. Multiple mechanisms have been proposed to explain the role of high blood pressure in carcinogenesis. Maladaptive lipid peroxidation and increased reactive oxygen species are thought to be pathogenic factors [57]. In theory, the chronic changes that occur in prehypertension and clinical hypertension make the kidneys more likely to become cancerous [58]. In hypertensive states, upregulation of vasogenesis and hypoxia-inducing factors, including HIF-1α, might contribute to an increased risk of kidney cancer [19, 58, 59]. In addition, obesity is also one of the bridges between MS and kidney cancer. In obese patients, intracellular lipid accumulation, occurrence of stress reaction in mitochondria and endoplasmic reticulum, and tissue hypoxia was accompanied by changes in circulating adipokines, free fatty acids and oxygen levels [58]. On top of that, excessive obesity, especially visceral obesity, leads to a chronic state of inflammation throughout the body, which may be related to the release of inflammatory cytokines from adipose tissue, creating an environment that promotes tumor development [60, 61]. The pro-inflammatory cytokines IL-6 and IL-10 are strongly expressed in both renal cancer cells and stroma, and IL-10 levels are higher in more advanced tumors (pT3) [58, 62]. In vitro experiments have shown that adiponectin secreted by white adipose tissue can inhibit tumor growth by activating AMP-activated protein kinase (AMPK) and regulate downstream mTOR [63]. Patients with MS have reduced adiponectin levels, which increases the risk of kidney cancer development and metastasis [64]. In addition, leptin can mediate the proliferation of kidney cancer AKI-2 cells by activating extracellular signal-regulated kinase (ERK1/2) and janus kinase/signal transduction and transcriptional activator 3 (JAK/STAT3) signaling pathways, and elevated serum leptin levels and leptin receptor overexpression are associated with renal cancer invasion and progression [24, 65-67]. Therefore, the combination of a healthy diet, metformin, statins and even bariatric surgery with drugs that inhibit the relevant metabolic pathways may be one of the directions of future research [68, 69].

Summary

At present, more and more evidence prove that kidney cancer is significantly associated with MS, especially the two components of high blood pressure and obesity have been widely confirmed as risk factors for kidney cancer. The protective effect of metformin and statins on renal cancer and the protective effect of sorafenib and sunitinib on renal cancer patients provide lateral evidence for the relationship between MS and renal cancer. However, there is no consensus on the extent to which MS affects Fuhrman grading in patients with kidney cancer. The role of MS in the prognosis of patients with kidney cancer is unclear. It is also not clear as most of the evidence suggests MS has a negative impact on kidney cancer grade and prognosis, and MS can certainly cause pathologic damage to the kidneys. While each component of MS is known to be associated with cancer, whether the effects of these components are additive or synergistic is still debated. Therefore, these queries need to be addressed, with more clinical evidence and high-quality meta-analyses in the future.

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Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

YWW, YJS and MYZ: Conception, design of study, literature search and review, figure production, manuscript writting; JC: Supervision and approval for the final version of the manuscript.

Competing interests

The authors have no competing interest.

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