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Letter

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The Impact of Diabetes and Antidiabetics on the Obesity Paradox in Renal Cell Cancer

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Dear Editor,

With this letter, we aim to initiate a broader discussion about the impact of diabetes and antidiabetic medications on the so-called obesity paradox in renal cell carcinoma (RCC). RCC accounts for 3% of all cancer cases, and in Europe, 54,054 deaths were reported in 2020, accounting for 30% of all RCC-related deaths worldwide. Meanwhile, the prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide, comprising about 90% of all diabetes cases [1, 2]. In 2019, 11% of women and 12.3% of men in Germany had a documented diagnosis of diabetes, which is one of the highest prevalence rates in Europe. Numerous studies suggest strong evidence that cancer incidence is increased in patients with T2DM [1].

The pathophysiological hypotheses to explain the link between diabetes or hyperglycemia and cancers rely on biological, particularly endocrine mechanisms involving insulin-resistance. In the genesis of T2DM, reduced insulin sensitivity plays a key role, inducing compensatory hyperinsulinaemia with an increased level of circulating insulin-like growth factors (IGF) [1, 2]. Moreover, diabetes has been significantly linked to an elevated risk of kidney cancer, as shown in a meta-analysis of 11 cohort studies [2]. Both cancer and diabetes treatments have also been shown to influence the relationship between diabetes and cancer-related outcomes [3].

A retrospective study identified a significant association between metformin use and a decreased risk of RCC. Additionally, a decreased risk of RCC was reported with increased cumulative duration of metformin use (inverse dose-response pattern) [4]. In animal models, certain sodium glucose cotransporter 2 inhibitors (SGLT2-I) have been associated with mammary, adrenal, testicular and renal neoplasms [2, 3, 5]. However, for exogenous insulin, thiazolidinediones, incretin-based drugs include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, no increased cancer risk has been observed [3].

Another important factor linked to RCC incidence is obesity. In several studies, a favourable RCC prognosis in terms of survival benefit was reported in patients with elevated BMI and is known as the "obesity paradox" [4]. One possible explanation is that patients with higher BMI may adequately preserve their fat and muscle mass, thus allowing a better nutritional status and potential survival advantage delaying the onset of cachexia [6].

An alternative explanation for the obesity paradox may be a different gene expression involving fatty acid metabolism

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genes. FASN (fatty acid synthase) is a gene that regulates de novo biosynthesis of fatty acids, an essential process for tumor growth. Interestingly, FASN is downregulated in patients with obesity and higher FASN expression is associated with worse survival. An upregulation of FASN gives cancer cells a survival advantage, making it a potential metabolic oncogene [7].

Further, BMI is an imperfect surrogate for biologically distinct body composition compartments, such as visceral adipose tissue and muscle mass, and inferences about the global metabolic state based on BMI are incomplete. Body composition can be measured indirectly using anthropometric measurements, such as BMI and abdominal circumference, or directly using computed tomography or dual-energy X-ray absorptiometry [8].

However, research on the relationship between diabetes and cancer risk is limited. Most studies have poor sensitivity to detect small associations, especially for specific cancer types. The use of various antihyperglycemic drugs in diabetic patients also complicates research, as adjustments to medication over time make it challenging to evaluate long-term outcomes [2].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.E.: project development, data analysis, and manuscript writing. H.Z.: data collection. D.L.D.: data generating. O.W.H.: manuscript editing.

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