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Characteristics and Outcomes of PD-1 Inhibitor–Associated Diabetes Mellitus: A Systematic Review of 158 Cases

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Abstract. Programmed cell death-1 (PD-1) inhibitor–associated diabetes mellitus is a rare but severe immune-related adverse event characterized by rapid β-cell destruction and abrupt onset of hyperglycaemia. This study aimed to systematically characterize the clinical features and outcomes of PD-1 inhibitor–associated diabetes mellitus through a pooled analysis of reported cases. Literature was retrieved from PubMed, Springer, China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Periodic Database, and the Chinese Journal of Diabetes Mellitus, and clinical characteristics, laboratory findings, treatment patterns, and outcomes of 158 patients from 83 eligible studies were systematically extracted and analyzed. The results showed that the mean age at onset was 60.88 ± 12.8 years, with a male predominance (70.9%). Patients presented with markedly elevated glucose levels despite only moderately increased HbA1c levels, accompanied by significantly reduced C-peptide levels, indicating severe insulin deficiency. Diabetic ketoacidosis (DKA) occurred in 85.1% of patients. No significant differences were observed among different PD-1 inhibitors in terms of clinical characteristics or outcomes, supporting a class effect. Compared with non-DKA patients, those with DKA were younger and had higher glucose levels but lower HbA1c and C-peptide levels, suggesting a more abrupt onset of β-cell failure. However, DKA was not associated with higher discontinuation or mortality rates, and no significant predictors of treatment discontinuation were identified. Overall, PD-1 inhibitor–associated diabetes mellitus demonstrates clinical features resembling fulminant type 1 diabetes, highlighting the importance of early recognition and prompt insulin treatment in clinical management.

Keywords: PD-1 inhibitors, Immune-related adverse events, Diabetes mellitus, Diabetic ketoacidosis

1. Introduction

In recent years, immune checkpoint inhibitors (ICIs), especially PD-1 inhibitors, have made breakthrough progress in the field of cancer treatment. Nivolumab, pembrolizumab, and other PD-1 inhibitors are increasingly applied across multiple malignancies, including melanoma and lung cancer. It has significantly improved the survival prognosis of patients, gradually becoming an important drug for current tumor treatment [1, 2].

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However, with the widespread use of PD-1 inhibitors, cases of immune related adverse events (irAEs) related to them have gradually been reported. These adverse reactions mainly stem from excessive activation of the immune system, affecting multiple organ systems including the skin, gastrointestinal tract, liver, and endocrine system. Among them, endocrine system toxicity is more common, such as thyroid dysfunction and pituitary inflammation [3, 4]. In contrast, although the incidence of inhibitor related diabetes (ICI-DM) at immune checkpoint is low, the disease often progresses rapidly, even endangering the patient's life [5].

A major clinical characteristic of ICI-DM is the sudden destruction of pancreatic β-cell function, resulting in profound hyperglycaemia and marked insulin deficiency [5]. Unlike conventional type 2 diabetes, patients frequently present with extremely elevated glucose levels despite only modest increases in HbA1c, reflecting the acute nature of disease onset. These metabolic features resemble fulminant type 1 diabetes [6]. However, the clinical spectrum, prognostic factors, and differences among PD-1 inhibitors remain incompletely understood.

With the continuous expansion of the scope of PD-1 inhibitor use and the number of patients, the risk of ICI-DM may gradually increase. Therefore, it is of great clinical significance to identify the characteristics of diabetes patients caused by the use of PD-1 inhibitors. Meanwhile, further research is needed to investigate whether there are clinical phenotype or prognostic differences between different PD-1 monoclonal antibodies, and whether factors such as DKA affect patient treatment decisions and prognosis.

Therefore, based on the reported cases, this study systematically analyzed the clinical characteristics of PD-1 inhibitor related diabetes, including the characteristics of blood glucose metabolism, changes in pancreatic islet function, and clinical outcomes, in order to deepen the understanding of the disease and provide a basis for clinical diagnosis and treatment decisions.

2. Method

Literature was retrieved from the following platforms and databases PubMed, Springer, China National Knowledge Infrastructure (CNKI), Wanfang, VIP Chinese Science and Technology Periodic Database, and Chinese Journal of Diabetes Mellitus. PD-1 inhibitors, immune checkpoint inhibitors, nivolumab, pembrolizumab, diabetes, type 1 diabetes and fulminant type 1 diabetes were the key words. Retrieve the literature related to diabetes caused by PD-1 inhibitor, and refer to the original text one by one, and eliminate the repeated reports or clinical reports of cases from the same literature and review. A total of 83 eligible studies was obtained, with a total of 158 patients [5, 7-88].

This study used a self-designed Excel data extraction table to record patient related information, including gender, age, tumor type, PD-1 inhibitor type, blood glucose metabolism characteristics, pancreatic islet function changes, and clinical outcomes. Metric data that conforms to a normal distribution are represented by $\bar{x}\pm s$, while metric data that does not conform to a normal distribution are represented by the median (interquartile range) [M (Q1, Q3)]. Comparisons among multiple groups were performed using the Kruskal–Wallis test, while comparisons between two groups were performed using the Mann–Whitney U test. Categorical variables were analyzed using Fisher's exact test. A p value <0.05 was considered statistically significant.

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3. Result

3.1. Basic characteristics statistics of patients

By searching for relevant keywords in the database, a total of 83 articles (158 patients) were obtained. By organizing patient characteristic related data, the following results were obtained.

Table 1. Basic characteristics statistics of patients

	Number	Percentage/Average/IQR
Gender		
Male	112	70.9%
Female	46	29.1%
Age	158	60.88±12.8
Tumor type		
Lung cancer	49	31%
Melanoma	40	25.3%
Renal cancer	10	6.3%
Esophageal cancer	7	4.4%
Liver cancer	7	4.4%
Gastric cancer	6	3.8%
Bladder cancer	4	2.5%
Others cancer	35	22.3%
PD-1 inhibitor type		
Nivolumab	51	33.6%
Pembrolizumab	46	30.3%
Tislelizumab	16	10.5%
Sintilimab	14	9.2%
Camrelizumab	12	7.9%
Toripalimab	5	3.3%
Serplulimab	3	1.9%
Combination therapy	5	3.3%
Outcome		
Fasting glucose	64	16.7 mmol/L (IQR 13.2–22.4)

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Table 1. (continued)

Postprandial glucose	52	28.3 mmol/L (IQR 22.1–36.5)
Random glucose	98	30.1 mmol/L (IQR 21.0–43.8)
HbA1c	123	8.1% (IQR 7.4–8.8)
C-peptide	114	0.14 ng/mL (IQR 0.05–0.37)
Examination		
DKA incidence	97	85.1%
Low C-peptide ratio	21	18.4%
Antibody positive rate	50	46.3%
Discontinuation rate	43	58.9%
Mortality rate	8	6.5%

In Table 1, a total of 158 patients with PD-1 inhibitor–associated diabetes was included. The mean age was 60.88±12.8 years. There was a clear male predominance (112 males and 46 females).

The most common underlying malignancies were lung cancer (n=49) and melanoma (n=40), followed by renal cancer (n=10), esophageal cancer (n=7), liver cancer (n=7), gastric cancer (n=6), bladder cancer (n=4), and other cancers (n=35).

Among 152 patients with available treatment data, the most frequently used PD-1 inhibitors were nivolumab (n=51) and pembrolizumab (n=46), followed by tislelizumab (n=16), sintilimab (n=14), camrelizumab (n=12), toripalimab (n=5), serplulimab (n=3), and combination therapy (n=5).

At the time of diabetes onset, patients presented with markedly elevated glucose levels. Despite severe hyperglycaemia, HbA1c was only moderately elevated at 8.1%. C-peptide levels were markedly reduced, with a median of 0.14 ng/mL, indicating profound insulin deficiency.

Diabetic ketoacidosis (DKA) occurred in 85.1% of patients (97/114). A subset of patients (18.4%, 21/114) had extremely low C-peptide levels (<0.02ng/mL). Autoantibody positivity was observed in 46.3% (50/108). Overall, treatment discontinuation occurred in 58.9% (43/73), and the mortality rate was 6.5% (8/124).

3.2. Discordance between hyperglycaemia and HbA1c

A notable feature of PD-1 inhibitor–associated diabetes was the discordance between extremely high glucose levels and only modest elevation of HbA1c. The normal situation is that long-term high blood sugar leads to high HbA1c. Although ICI-DM patients have significantly elevated blood glucose levels, their HbA1c levels are relatively low, and their C-peptide levels are significantly reduced, indicating a rapid loss of pancreatic beta cell function in a short period of time. This inconsistency of "hyperglycemia low HbA1c low C-peptide" supports the acute onset characteristics of the disease, which is similar to fulminant type 1 diabetes, and also explains the high incidence of DKA.

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3.3. Comparison of different PD-1 monoclonal antibodies

Comparisons among major PD-1 inhibitors (nivolumab, pembrolizumab, tislelizumab, sintilimab, and camrelizumab) in Table 2 showed no statistically significant differences in clinical characteristics. Due to extremely small sample sizes, toripalimab, serplulimab, and combination therapy groups were excluded from comparative statistical analyses. These findings suggest that the clinical phenotype of ICI-related diabetes is consistent across different PD-1 inhibitors, supporting a class effect rather than drug-specific toxicity.

Table 2. Different indicators in patients with different PD-1 monoclonal antibodies

	Nivolumab (n=51)	Pembrolizumab (n=46)	Tislelizumab (n=16)	Sintilimab (n=14)	Camrelizumab (n=12)	P-value
Age (years)	61.9 (n=51)	62.4 (n=46)	59.8 (n=16)	59.4 (n=14)	59.4 (n=12)	0.62
Random glucose (mmol/L)	39.1 (n=31)	35.3 (n=27)	38.4 (n=8)	43.2 (n=9)	34.0 (n=6)	0.28
HbA1c (%)	8.28 (n=34)	8.06 (n=33)	8.02 (n=12)	7.94 (n=14)	8.22 (n=9)	0.74
Fasting C-peptide (ng/mL)	0.50 (n=23)	0.21 (n=31)	0.18 (n=10)	0.12 (n=13)	0.24 (n=8)	0.19
DKA	80.0% (24/30)	88.2% (30/34)	87.5% (7/8)	92.3% (12/13)	77.8% (7/9)	0.53
Discontinuation	45.8% (11/24)	54.5% (12/22)	50.0% (3/6)	50.0% (3/6)	50.0% (2/4)	0.67
Mortality rate	5.9% (3/51)	8.7% (4/46)	6.3% (1/16)	0% (0/14)	0% (0/12)	0.74

3.4. Comparison of DKA group and non DKA group

Among 114 patients, 97 presented with DKA and 17 did not. Detailed comparisons between the DKA and non-DKA groups are shown in Table 3. Compared with non-DKA patients, those with DKA were significantly younger (58.61 vs. 65.24 years, p=0.021) and had higher glucose levels (39.28 vs. 31.06 mmol/L, p=0.013), but lower HbA1c (8.10% vs. 8.68%, p=0.008) and markedly reduced C-peptide levels (0.160 vs. 0.686 ng/mL, p<0.001).There were no significant differences in treatment discontinuation (60.4% vs. 66.7%, p=0.62) or mortality rates (6.2% vs. 11.8%, p=0.41) between the two groups.

Table 3. Different indicators of DKA group and non DKA group

	DKA group	non DKA group	P-value
Age (years)	58.61 (n=97)	65.24 (n=17)	0.021
Random glucose (mmol/L)	39.28 (n=72)	31.06 (n=10)	0.013
HbA1c（%）	8.10 (n=90)	8.68 (n=17)	0.008
Fasting C-peptide (ng/mL)	0.160 (n=46)	0.686 (n=11)	<0.001
Discontinuation rate	60.4% (29/48)	66.7% (8/12)	0.62
Mortality rate	6.2% (6/97)	11.8% (2/17)	0.41

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3.5. Comparison between immunotherapy continuation and discontinuation groups

In Table 4, no significant differences were observed between patients who discontinued and those who continued immunotherapy in terms of age, glucose levels, HbA1c, C-peptide, DKA incidence, or mortality (all $p > 0.05$). Additionally， a trend toward a higher proportion of males was observed in the continuation group (83.3% vs. 62.8%, p=0.06). These findings suggest that no clear clinical predictors of treatment discontinuation were identified.

Table 4. Characteristics of drug continuation group and discontinuation group

	Discontinuation (43)	Continuation (30)	P-value
Age(years)	59.7 (n=43)	60.7 (n=30)	0.77
Fasting glucose (mmol/L)	22.15 (n=24)	22.86 (n=2)	0.91
Postprandial glucose (mmol/L)	24.08 (n=3)	25.32 (n=3)	0.88
Random glucose (mmol/L)	34.96 (n=26)	37.71 (n=27)	0.53
HbA1c (%)	8.24 (n=40)	8.17 (n=28)	0.82
Fasting C-peptide (ng/mL)	0.266 (n=34)	0.228 (n=17)	0.48
2h C-peptide ng/mL	0.227 (n=21)	0.124 (n=5)	0.21
Male ratio	62.8% (27/43)	83.3% (25/30)	0.06
DKA ratio	77.8% (28/36)	83.3% (20/24)	0.69
Antibody positive ratio	16.2% (6/37)	29.2% (7/24)	0.13
Mortality ratio	9.3% (4/43)	0% (0/30)	0.11

4. Discussion

Based on 158 reported cases from 83 studies, this review comprehensively summarized the clinical manifestations and outcomes of PD-1 inhibitor–associated diabetes mellitus. Although uncommon, ICI-DM is clinically important because of its rapid onset, severe insulin deficiency, and high frequency of diabetic ketoacidosis. With the expanding use of PD-1 inhibitors in oncology, improving recognition of this complication is increasingly relevant for clinical management. The present study identified several characteristic metabolic and clinical patterns that may assist clinicians in early diagnosis and treatment decisions.

One of the most important findings of this study is that ICI-DM patients exhibit a significant separation phenomenon of "high blood glucose low HbA1c". The research results showed that patients' random blood glucose levels significantly increased at the onset of the disease, with a median of over 30 mmol/L, but HbA1c levels were only moderately elevated. At the same time, the level of C-peptide significantly decreased, indicating a rapid loss of pancreatic beta cell function in a short period of time. This combined feature of "severe hyperglycemia, limited increase of HbA1c, and significant decrease of C-peptide" suggests that ICI-DM is different from the chronic progression mode of traditional type 2 diabetes. It is more similar to the acute onset process of fulminant type 1 diabetes. Since HbA1c reflects the average blood glucose level over the past 2-3 months, even if patients experience severe hyperglycemia, HbA1c may not have significantly increased in the case of rapid destruction of beta cells in the short term [89]. This feature has significant value for clinical identification of ICI-DM.

Another finding of this study is that the incidence of DKA in ICI-DM patients is extremely high. Among patients with available DKA data, 85.1% (97/114) developed DKA, which was significantly

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higher than the general type 1 diabetes population [90]. This suggests that PD-1 inhibitor associated pancreatic injury is highly invasive and rapidly progressing. Further comparison between the DKA group and the non DKA group revealed that patients in the DKA group were younger, had higher blood glucose levels, and lower HbA1c and C-peptide levels. This suggests that DKA patients may have experienced a more rapid and severe process of beta cell dysfunction. It is worth noting that although the metabolic disorders in the DKA group were more severe, their mortality and discontinuation rates did not significantly increase. This suggests that as long as insulin treatment can be identified and administered in a timely manner, most patients can still achieve good short-term control effects.

This study also found that no significant clinical differences were observed between different PD-1 inhibitors. There were no statistically significant differences in blood glucose levels, HbA1c, C-peptide, incidence of DKA, discontinuation rate, and mortality rate among the groups, whether nivolumab, pembrolizumab, tislelizumab, sintilimab, or camrelizumab. This suggests that ICI-DM may be a class effect caused by PD-1 pathway blockade, rather than a unique side effect of a particular drug. Mechanistically, PD-1 inhibitors exert anti-tumor effects by relieving T cell immune suppression and enhancing autoimmune responses. Therefore, it is reasonable for different PD-1 inhibitor drugs to cause similar autoimmune damage to beta cells. This result also suggests that clinicians need to be alert to the occurrence of ICI-DM when using any PD-1 inhibitor, not just limited to a single drug.

In addition, this study found a lack of clear predictive factors for drug discontinuation. There were no significant differences in age, blood glucose, HbA1c, C-peptide, DKA incidence, and mortality between the continuing immunotherapy group and the discontinuation group. Although the proportion of males in the continued treatment group was higher, it did not reach statistical significance. This result has certain clinical significance. In practical clinical practice, whether to permanently discontinue immunotherapy after ICI-DM has always been an important issue of clinical concern. The results of this study suggest that after sufficient insulin therapy and metabolic control, some patients can still continue to receive PD-1 inhibitor treatment. Due to the irreversible damage of β-cell caused by ICI-DM, even if PD-1 inhibitors are discontinued, it is difficult to restore pancreatic function. Therefore, for patients who benefit significantly from tumor treatment, continuing immunotherapy may still be reasonable. Of course, this still requires a comprehensive assessment based on the patient's tumor status, metabolic control, and individualized risk.

Compared with other PD-1 inhibitor related adverse reactions, ICI-DM has some unique characteristics. Common endocrine irAEs, such as thyroid dysfunction, pituitary inflammation, or adrenal insufficiency, typically progress relatively slowly [91]. Some patients may still experience some degree of recovery after glucocorticoid treatment. ICI-DM is characterized by acute onset, rapid metabolic deterioration, and severe insulin deficiency. Once beta cells are destroyed, most patients require long-term or even lifelong insulin therapy. This irreversibility is significantly different from other endocrine immune related adverse reactions.

At present, the specific mechanism of ICI-DM is not fully understood. Current research suggests that the PD-1 pathway plays an important role in maintaining peripheral immune tolerance. When PD-1 inhibitor blocks this pathway, it can lead to over activation of autoreactive T cells, thus attacking pancreatic islet β-cell and inducing autoimmune diabetes [6,92]. In addition, genetic susceptibility may also be involved in the occurrence of diseases. Some studies have found that some ICI-DM patients carry HLA genotypes related to type 1 diabetes, especially HLA-DR4 [83]. At the same time, about half of the patients in this study have positive autoantibodies related to diabetes, which also indicates that some patients may have potential autoimmune susceptibility

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background. However, since not all patients develop antibody positivity, the mechanism of ICI-DM may also involve other complex immune processes.

This study has certain advantages. First, the number of cases included in this study is relatively large, which is one of the more systematic summaries of PD-1 inhibitor related diabetes. Secondly, this study included both Chinese and English literature databases, which improved case coverage and population representativeness. In addition, this study not only analyzed the overall clinical characteristics, but also further compared the differences between different PD-1 inhibitors, DKA and non DKA patients, as well as between continuing treatment and discontinuing treatment, providing more reference information for clinical management.

Undeniably, this study still has certain limitations. Firstly, this study is mainly based on case reports and retrospective research, which are susceptible to publication bias and report bias. Severe cases are more likely to be reported, so the incidence of DKA and other results may be overestimated to some extent. Secondly, there are differences in the completeness of case data among different literature, with some patients lacking complete laboratory data, antibody testing, or follow-up information, resulting in limited sample sizes for some analyses. Thirdly, there is heterogeneity among different studies in terms of blood glucose testing time, laboratory methods, and treatment records, which may also affect the stability of statistical results. In addition, some PD-1 inhibitors such as toripalimab and serplulimab have a relatively small number of cases, which may limit the statistical efficacy of comparing differences between different drugs. Finally, due to the lack of long-term follow-up data in most cases, further research is needed on the long-term metabolic outcomes and tumor prognosis of ICI-DM patients.

Further large-scale and prospective studies are needed in the future to clarify the incidence, risk factors, and long-term prognosis of ICI-DM. Especially, it is necessary to explore early predictive biomarkers, including HLA genotypes, autoantibody profiles, and dynamic immunological indicators, to achieve early identification of high-risk patients. Furthermore elucidating the immune mechanism of ICI-DM can also provide a theoretical basis for the prevention and personalized management of this disease.

5. Conclusion

PD-1 inhibitor–associated diabetes is characterized by rapid β-cell destruction, severe hyperglycaemia, and a high incidence of DKA, with a notable discordance between glucose and HbA1c levels. The clinical phenotype is consistent across different PD-1 inhibitors, and outcomes are not determined by drug type or DKA status. These findings highlight the importance of early recognition and individualized clinical management of this rare but serious immune-related adverse event.

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