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Review

Immune Checkpoint Inhibitor-Associated Diabetes Mellitus: Future Perspectives and Emerging Therapies

Jean-Luc Karavendzas [1,2], Anna Galligan [1], Melissa H. Lee [1,2], Anthony Dowling [2,3], Balasubramanian Krishnamurthy [1,2,4] and Richard J. MacIsaac [1,2,5,*]

[1] Department of Endocrinology & Diabetes, St Vincent's Hospital Melbourne, Fitzroy, VIC 3065, Australia; melissa.lee@svha.org.au (M.H.L.)
[2] Department of Medicine, The University of Melbourne, Fitzroy, VIC 3065, Australia; anthony.dowling@svha.org.au
[3] Department of Medical Oncology, St Vincent's Hospital Melbourne, Fitzroy, VIC 3065, Australia
[4] Immunology and Diabetes Unit, St Vincent's Institute of Medical Research, Fitzroy, VIC 3065, Australia
[5] Australian Centre for Accelerating Diabetes Innovations, University of Melbourne, Parkville, VIC 3052, Australia
* Correspondence: r.macisaac@unimelb.edu.au

Abstract

Objective: Current knowledge surrounding the diagnosis and mechanisms that result in immune checkpoint inhibitor-associated diabetes (ICI-DM) remain to be fully defined. We present clinical vignettes of patients that have presented to our hospital to illustrate the heterogenous clinical profiles that patients with ICI-DM can experience. We also provide an update on ICI-DM, focusing on current and future perspectives and emerging therapies. Methods: We performed a retrospective review of the electronic records of five ICI-DM patients who presented to St. Vincent's Hospital Melbourne between 2020 and 2024, with patients identified from the hospital endocrinology and oncology databases. We also performed a literature review via a PubMed search using the keywords "checkpoint inhibitors" and "diabetes" between the years 2015 and 2025 to allow us to collate a descriptive review on ICI-DM. Results: Our cases show some heterogeneity in presentation, with biochemical evidence of diabetic ketoacidosis (DKA) in 4/5 patients, presentation 18–253 days (median 47 days) from ICI commencement, HbA1c 59–78 mmol/mol (median 66 mmol/mol), and c-peptide 0.06–0.77 pmol/mL (median 0.09 pmol/mL). Islet autoantibodies were present in 4/5 cases and high-risk HLA alleles identified in 1/2 tested patients. The findings from our descriptive review support a similar heterogeneity in ICI-DM presentations. Inconsistent diagnostic criteria for ICI-DM were noted with low c-peptide being the most common biochemical presentation. Pancreatic volume is emerging as a useful predictive marker of ICI-DM development. We found no reports of the reversal of ICI-DM with immunosuppression in humans, although recent preclinical studies suggest that this approach is feasible. Conclusions: Diagnostic criteria should include new-onset hyperglycaemia with low paired c-peptide, and may be supported with T1DM-associated autoantibodies and evidence of pancreatic atrophy on imaging. Further research is needed in the realm of predicting ICI-DM and considering the role of immunosuppression as a treatment modality.

Keywords: immune checkpoint therapy; diabetes mellitus; immune-related adverse events; ketoacidosis; CTLA-4; PD-L1; JAK1 selective inhibitor

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1. Introduction

In recent years, immunotherapy has become an established treatment to traditionally accepted chemotherapy, radiotherapy and surgery for the treatment of various malignancies. Immune checkpoint inhibitors (ICIs) in particular have become increasingly utilised in the form of monoclonal antibody therapies that target regulatory cell surface checkpoint molecules and unleash the immune response against cancer. ICIs typically target the molecule, programmed cell death protein-1 (PD-1), and its ligand, programmed death-ligand 1 (PD-L1), as well as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) [1]. Inhibition of these two molecular pathways via checkpoint blockade therapy has been shown to have significant clinical benefits in many neoplasms, notably melanoma and non-small-cell lung cancer, by the reversal of physiologic T-cell tolerance [1,2].

Lifting the brakes on the immune system, however, does not come without risks. Immune-related adverse events (irAEs) in many organ systems are observed in patients commenced on ICIs, most commonly skin, gastrointestinal, and thyroid toxicities [2]. Endocrinopathies are notable among irAEs in that the hormonal deficiencies resulting from immune injury to endocrine tissue tend to be permanent and non-responsive to immunosuppression [3,4]. Immune checkpoint inhibitor-associated diabetes mellitus (ICI-DM) is believed to be a result of the autoimmune destruction of pancreatic islet β-cells, resulting in insulin deficiency and hyperglycaemia [5]. The classic presentation is that of diabetic ketoacidosis (DKA) or acute hyperglycaemia with low or undetectable c-peptide levels, suggestive of insufficient insulin production [6]. In contrast to spontaneous type 1 diabetes (T1DM), ICI-DM can present with a more rapid and fulminant onset after the administration of checkpoint inhibitor therapy [3]. As such, it usually presents with either a mildly elevated or even normal glycated haemoglobin, reflecting a shorter duration of pathology prior to presentation [5].

In the last 10 years, case reports of ICI-DM demonstrate heterogeneity of presentation [5–9]. The classic, fulminant autoimmune diabetes is well described, but patients may also present with subacute autoimmune diabetes, exocrine pancreatitis, or the presentation may be confounded by factors such as concomitant glucocorticoid use or pre-existing type 2 diabetes mellitus (T2DM) [4]. Identifying ICI-DM is crucial so that insulin therapy can be appropriately commenced in patients with this immunotherapy-associated β-cell toxicity.

We present several clinical vignettes of patients that have presented to our hospital to illustrate the heterogenous clinical profiles that patients with ICI-DM can experience. We also provide an update on ICI-DM, focusing on current and future perspectives and emerging therapies.

2. Materials and Methods

We performed a retrospective review of the electronic records of five ICI-DM patients who presented to St. Vincent's Hospital Melbourne between 2020 and 2024, with patients identified from the hospital endocrinology and oncology databases. A waiver to obtain a formal ethics application and consent from the patients or their next of kin for the purposes of this report was granted by the SVHM research office.

We performed a literature review via the PubMed database to identify relevant studies. The search strategy included a combination of the free-text keywords "checkpoint inhibitor" and "diabetes", as well as the abbreviations "ICI-DM", "CIADM", and "CPI-DM". We prioritised the inclusion of original research, select case reports of interest, and existing review articles between the years of 2015 and 2025. Single case reports of typical ICI-DM presentations were excluded. A total of 131 studies were identified as relevant to our review. A PRISMA flow diagram is included in Appendix A.

3. Results

Illustrative Case Vignettes

A case series of five patients who were treated with ICIs and identified with ICI-DM at St Vincent's Hospital, Melbourne, Australia, between 2020 and 2024 is presented in this section. Patients were identified from the hospital oncology and endocrinology unit databases. Table 1 describes the patient demographics and relevant clinical characteristics. Table 2 describes their diabetes-related clinical presentation, biochemical results, and autoantibody status.

Table 1. Patient demographics and relevant clinical characteristics.

Patient	Age/Sex	Tumour Type	Checkpoint Inhibitor	Time to Diabetes Onset from ICI Commencement	Relevant Past Medical History	Other irAEs
1	70/F	Mesothelioma	Ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1)	18 days	-	-
2	24/M	Astrocytoma	Cadonilimab (anti-PD-1/CTLA-4)	64 days	-	Colitis
3	59/F	NSCLC	Pembrolizumab (anti-PD-1)	22 days	SLE, Hashimoto's thyroiditis, T2DM (HbA1c 9.4% pre-ICI commencement)	-
4	52/F	NSCLC	Atezolizumab (anti-PD-L1)	253 days	-	Thyroiditis
5	62/M	Colorectal adenocarcinoma	Pembrolizumab (anti-PD-1)	47 days	-	-

ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; M, male; F, female; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus; HbA1c, glycated haemoglobin.

Patients were aged between 24 and 70 years (mean 53.4, median 59) and presented within 18 and 253 days of ICI commencement (mean 80.8 days, median 47 days). Four of the patients presented to the emergency department with DKA, and the remaining patient was diagnosed incidentally. Glycated haemoglobin (HbA1c) on presentation ranged from 59 to 78 mmol/mol or 7.6 to 9.3% (mean 67.6 mmol/mol (8.36%), median 66 mmol/mol (8.2%)) with a low c-peptide for paired glucose on presentation, between 0.06 and 0.77 pmol/mL (mean 0.23, median 0.09).

Patients 1 and 2 were treated with combination anti-PD-1 and anti-CTLA-4 therapy, (patient 2 in the setting of a clinical trial) and patients 3 and 5 with anti-PD-1 therapy alone. Diagnosis of ICI-DM was made after a thorough review by the hospital endocrinology team, identified as new-onset insulin-deficient diabetes after ICI commencement, with ruling out of other causes of hyperglycaemia, and supported by autoantibody positivity. None of the patients in our series were receiving glucocorticoid treatment at the time of diagnosis.

Table 2. Details of diabetes presentation.

Patient	Diabetes Presentation	Biochemistry on Presentation *	HbA1c (mmol/mol (%))	Autoantibodies	HLA
1	DKA	Glucose > 60 mmol/L Ketones 7.6 mmol/L pH 7.06 C-peptide 0.15 pmol/mL HCO_3 8 mmol/L Anion gap 36 Lactate 4.6 mmol/L	59 (7.6%)	GAD > 2000 U/mL (<5) ZnT8 63 RU/mL (<10) IA-2 < 7.5 U/mL (<7.5)	Neutral-risk alleles: DQA1*3:03:01 DQB1*3:02:02
2	DKA	Glucose 30.0 mmol/L Ketones 6 mmol/L pH 7.02 C-peptide 0.08 pmol/mL HCO_3 8 mmol/L Anion gap 28 Lactate 2.4 mmol/L	66 (8.2%)	GAD 147.0 U/mL (<5) ZnT8 < 10 RU/mL (<10) IA-2 < 7.5 U/mL (<7.5)	High-risk alleles: DQA1*5:01:01 DQB1*2:01:01
3	DKA	Glucose 23.8 mmol/L Ketones 7.4 mmol/L pH 7.15 C-peptide 0.06 pmol/mL HCO_3 12 mmol/L Anion gap 28 Lactate 2.3 mmol/L	75 (9.0%)	GAD 1960.0 U/mL (<5) IA-2 44.8 U/mL (<7.5)	Not available
4	Acute hyperglycaemia	Glucose 15.3 mmol/L Ketones 0.1 mmol/L C-peptide 0.77 pmol/mL Anion gap 15	60 (7.7%)	GAD 47.0 U/mL (<5) IA-2 < 7.5 U/mL (<7.5) Insulin ab—undetected	Not available
5	DKA	Glucose 26.0 mmol/L Ketones 6.2 mmol/L pH 7.14 C-peptide 0.09 pmol/mL HCO_3 9 mmol/L Anion gap 25 Lactate 2.2 mmol/L	78 (9.3%)	GAD < 5 U/mL (<5) IA-2 < 7.5 U/mL (<7.5)	Not available

HLA, human leukocyte antigen; DKA, diabetic ketoacidosis; GAD, glutamic acid decarboxylase; IA-2, islet antigen 2; ZnT8, zinc co-transporter 8. * Biochemistry reference ranges: Glucose 3.9–5.8 mmol/L, ketones < 0.6 mmol/L, c-peptide < 0.7 pmol/mL for fasting, non-obese, normoglycaemic subjects, HCO_3 21–28 mmol/L, anion gap 10–20, lactate 0.5–1.6 mmol/L. C-peptide levels were measured using an automated two-step chemiluminescent microparticle immunoassay (Abbott Laboratories, Macquarie Park, NSW, Australia). The reference range from manufacturer was 260–1718 pmol/L. The limit of detection was 10 pmol/L. Precision CV was 2.2% at 311 pmol/L and 2.0% at 1277 pmol/L.

Patient 4 was treated with anti-PD-L1 therapy and presented as an outpatient with incidental asymptomatic hyperglycaemia prior to a routine PET scan, not requiring hospitalisation. This occurred 36 weeks following ICI commencement (which was the longest duration in our case series), and the c-peptide level was the most robust at 0.77 pmol/mL, with a paired glucose of 15.3 mmol/L. Repeat c-peptide testing was not performed; however, a decrease would likely have been expected [10]. While it is less clear that her presentation represented an autoimmune diabetes compared with the other patients, we have decided to include it here as a case of ICI-DM given the elevated GAD autoantibodies, low C-peptide for paired glucose, and lower HbA1c at presentation compared with pre-ICI commencement (7.7% vs. 9.4%), suggestive of acute hyperglycaemia rather than worsening T2DM. The patient was initially treated as T2DM and commenced on metformin; however, this was ceased upon the return of the c-peptide level and autoantibody results approxi-

mately one month after initial presentation. There was later a period of poor glycaemic control in the context of glucocorticoid commencement, with a HbA1c ten months after presentation at 99 mmol/mol (11.3%). Upon weaning of steroids, she was managed with six units of daily basal insulin and 6–10 units of rapid-acting insulin with meals, the lowest insulin requirement of the cases presented.

Patient 3 had pre-existing type 2 diabetes and reported sudden elevated home blood glucose readings in the range of 20–30 mmol/L in the four days leading up to DKA presentation, with previous readings in the range of 6–8 mmol/L. This patient had a relevant autoimmune history of SLE and Hashimoto's thyroiditis, and a pre-ICI HbA1c of 9.4%. Given this history, pre-treatment islet autoantibody testing may have picked up either type 1 diabetes or increased risk for islet autoimmunity.

Two patients developed additional irAEs; patient 2 developed immunotherapy-related colitis 73 days after presenting with ICI-DM (137 days after ICI commencement) and was treated with vedolizumab alone. Patient 4 developed immunotherapy-related thyroiditis 113 days prior to ICI-DM presentation (140 days after ICI commencement) and was commenced on levothyroxine.

Each patient underwent subsequent autoimmune antibody screening with the analysis of known T1DM autoantibodies: anti-glutamic acid decarboxylase (GAD), anti-islet antigen 2 (IA-2), with anti-zinc co-transporter 8 (ZnT8) additionally tested in patients 1 and 2 and anti-insulin antibodies tested in patient 4. Patients 1, 2, 3 and 4 all had elevated GAD antibodies, with patient 1 also presenting with elevated ZnT8 and patient 3 with elevated IA-2 antibody levels. Patient 5 did not return elevated levels of any screened antibodies. None of the patients had pre-treatment islet autoantibodies available. HLA typing was performed for patients 1 and 2; patient 1's haplotype was DQA1*3:03:01+DQA1*3:03:01~DQB1*3:01:02+DQB1*3:02:02. Patient 2's haplotype was DQA1*1:03:01+DQA1*5:01:01~DQB1*2:01:01+DQB1*6:03:01, with DQA1*5:01:01 and DQB1*2:01:01 being high-risk alleles for type 1 diabetes [11].

Of note, patients 1, 2, and 3 each suffered a second episode of DKA, 33 days, 85 days, and 8 days following their initial presentations, respectively, reflecting the difficulty in achieving glycaemic control in ICI-DM. For patient 1, this was in the setting of withheld insulin doses and reduced oral intake due to an obstructed food bolus requiring endoscopic intervention, as well as insufficient sick day education. For patient 2, this appeared to be in the setting of alcohol intake with reduced insulin dosing. Patient 3 was initially euglycaemic but developed progressively elevated glucose and ketone levels at home, likely in the context of the return of appetite and insufficient insulin dose titration. After intensive diabetes education, patient 3 became proficient in flexible bolus dosing and achieved a HbA1c of 53 mmol/mol (7.0%) 2 months after initial presentation.

All patients in our case series were commenced on once-daily basal insulin and rapid-acting prandial insulin. Insulin requirements varied and were subject to long-term titration. Continuous glucose-monitoring devices were used by all patients. Patient 2 transitioned from multiple daily injections to insulin pump therapy 8 months following initial presentation. Patients 4 and 5 required intermittent treatment with dexamethasone as part of chemotherapy protocols later in their treatment courses, and despite planned insulin dose increases, hyperglycaemia progressed as evidenced by rising HbA1c and self-monitored glucose levels.

The clinical features observed in this case series align with what has been reported in the literature. DKA with low c-peptide was the most common initial biochemical presentation observed, and with the exception of patient 4, the cases presented within a few weeks of ICI commencement. For the patients positive to T1DM autoantibodies, GAD represented the majority of elevated markers. Given that HLA data was only available for

2/5 patients, we are unable to comment on commonly observed haplotypes. Interestingly, one patient had high titres of autoantibodies (GAD and ZnT8) despite not having high-risk HLA class II alleles. Formal statistical analysis was not performed due to the small sample size.

4. Discussion

4.1. Epidemiology and Clinical Features of ICI-DM

ICI-DM has been reported in 0.2–1.9% of patients treated with ICIs [12–15]. DKA at presentation of ICI-DM is seen in 69.7–76% of cases [3,8,16]. The frequency of autoantibody positivity in ICI-DM is lower than in T1DM, approximately 40–53% compared with an approximate 90% rate of seropositivity to at least one relevant autoantibody in T1DM [3,8,16–20]. Individuals positive to islet autoantibodies are more likely to initially present with DKA, and present earlier than their seronegative counterparts [3,8]. GAD autoantibodies are most frequently detected, with elevated titres seen in 39.7–51% of patients [3,8,16]. Genetic predisposition follows a similar pattern of reduced frequency with T1DM-susceptible HLA haplotypes present in 38–65% of ICI-DM patients as opposed to up to 90% of those with classical T1DM [3,8,16,21]. Similar high-risk alleles are observed in both conditions; HLA-DR4 appears to predominate and may represent a higher proportion of high-risk alleles in ICI-DM compared with spontaneous T1DM [14]. C-peptide may occasionally fall within the normal range on presentation, however, would be expected to be low for paired serum glucose concentration and fall below the reference range in all patients on repeat testing within weeks of diagnosis [10]. The majority of patients with ICI-DM have been treated with anti-PD-1, anti-PD-L1 therapy, or PD-1/CTLA-4 combination therapy, suggesting that the PD-1/PL-L1 axis is implicated in the pathogenesis [4]. Combination PD-1/CTLA-4 blockade has been implicated in a more rapid presentation and potentially higher incidence [9,16]. Very few cases of ICI-DM have been reported, however, from patients undergoing CTLA-4 inhibitor monotherapy. A small number of published reports describe diabetes presenting after treatment with the CTLA-4 inhibitor ipilimumab, but the pathophysiology is less well explained [22–24]. These reports unfortunately do not present in detail the associated presentation, clinical features, and biochemistry, and as such it is unclear whether these are true examples of an autoimmune insulin-deficient diabetes or whether hyperglycaemia can be attributed to another cause.

A notable feature of ICI-DM is its variability in presentation. While the majority of patients present with DKA, a significant minority do not, and instead may present with mild symptoms of hyperglycaemia or occasionally be detected incidentally. More severe and rapid presentations are associated with autoantibody positivity; however, to date, other factors do not seem to have a significant impact on speed of presentation [3]. There does not appear to be a major link between disease severity and HLA. Diagnostic criteria for ICI-DM are not consistent between cancer centres, and confounders or misdiagnoses are possible [25]. When identifying ICI-DM, it is important to rule out pre-existing and other causes of hyperglycaemia in ICI-treated oncology patients. The most common cause of elevated blood glucose in patients receiving cancer treatment is corticosteroid use, accounting for 68–76% of cases of new-onset hyperglycaemia [26]. T2DM patients also represent a significant cohort, representing 42–72% of cases of ICI-related hyperglycaemia [26]. ICI-related pancreatitis is identifiable by lipase elevation and radiological findings, and sometimes with evidence of pancreatic exocrine insufficiency [26]. If severe, this phenotype may lead to type 3c diabetes, resulting in ICI-related hyperglycaemia that is not caused by β-cell autoimmunity. Nevertheless, patients require insulin and are managed in the same fashion as other insulin-deficient diabetes patients. Case reports also exist of an ICI-related lipodystrophy resulting in hyperglycaemia, which may be important to

consider as a differential diagnosis [4,26]. In contrast to ICI-DM, such autoimmune loss of adipose tissue impacts insulin resistance and patients present with elevated c-peptide as well as triglycerides [4,26].

4.2. Future Perspectives

A number of papers have been published on ICI-DM; however, questions remain on how to approach diagnosis and management. As it currently stands, diagnostic criteria vary greatly across international guidelines and individual institutions but usually take into account any combination of new-onset hyperglycaemia following ICI commencement, autoantibody positivity, or evidence of insulin deficiency as part of their diagnostic criteria [3]. Establishing standardised diagnostic criteria for ICI-DM may be useful in preventing over-diagnosis. Higher incidence of this irAE is reported when relying solely on blood glucose levels to diagnose ICI-DM in the absence of other clinical features, and may result in the incorrect attribution of ICIs to other forms of diabetes or hyperglycaemia that develop during a patient's treatment course [25]. Consideration of the influence of corticosteroids is relevant when patients on checkpoint blockade therapy present with elevated blood glucose [3,4,25]. Furthermore, new-onset hyperglycaemia after ICI use may be due to the exacerbation of T2DM, ICI-related lipodystrophy, or pancreatitis, not necessarily representing the autoimmune destruction of pancreatic β-cells required for a true ICI-DM diagnosis and rather generalised metabolic dysfunction or non-selective pancreas toxicity [4,27]. Relying on autoantibody markers alone risks under-diagnosis as seropositive patients represent just over 40% of cases [3,20]. As such, it may be worthwhile to develop a set of diagnostic criteria for the accurate diagnosis of ICI-DM, encompassing new-onset hyperglycaemia with insulin deficiency and evidence of selective β-cell toxicity, while excluding other causes of hyperglycaemia that may be observed in this cohort of immunotherapy patients. C-peptide level is a key differentiating feature. Wu et al. suggest that new-onset hyperglycaemia combined with low c-peptide within one month of presentation are sufficient criteria for excluding differential diagnoses, with other clinical findings as supportive diagnostic features [26]. Further collaboration across institutions is needed in order to create a clear set of multidisciplinary guidelines for approaching accurate diagnosis, treatment regimens prioritising patient safety, and excluding non-autoimmune differentials for hyperglycaemia.

While unravelling our understanding of the pathophysiology of ICI-DM is of great importance, what may be more critical is learning to predict the onset of the disease to prevent patients from facing the life-threatening complications of DKA. Routine monitoring of blood glucose has not been useful in the prediction of ICI-DM, given that the onset of hyperglycaemia is typically acute without any preceding mild increase in blood glucose concentration [28,29]. No statistically significant difference in blood glucose could be demonstrated two weeks prior to diabetes onset in a study comparing 13 ICI-DM patients to matched controls [30]. Wu et al. describe several biomarkers that may be useful in the prediction of ICI-DM [10]. Pancreatic volumes were lower in ICI-DM patients prior to ICI exposure, and patients have additionally shown significantly higher GAD autoantibodies before treatment compared with controls [10]. Furthermore, ICI-DM patients were shown pre-ICI administration to have fever naïve CD4+ T-cells and a higher proportion of Th17 and memory CD4+ cells as well as elevated circulating cytokines, suggestive of a more active baseline immune system [31]. Further analysis of these markers in a larger cohort may assist in identifying patients who are high-risk.

Like other endocrinopathies, radiological changes in the pancreas can be observed in serial imaging performed before and during treatment in ICI-DM. Pancreatic atrophy is a characteristic finding in ICI-DM and in spontaneous T1DM [31,32]. Analysis of pancreatic

volumes on CT has been performed in at least four ICI-DM case series [7,10,33,34]. The most recent of the aforementioned studies suggests that imaging may in fact be more useful than islet autoantibody testing, with statistically significant decreases in pancreatic atrophy in a cohort of majority seronegative patients [34]. These case series have shown an average reduction in pancreatic volume at the last follow-up of 31–41% and up to 70% for at least one patient compared with baseline pre-ICI scans. Some cases have demonstrated a significantly lower baseline pancreatic volume in ICI-DM patients compared with controls; this may suggest a lower pancreatic reserve, putting patients at risk of developing diabetes, and presents itself as an area for further research [10]. In abdominal imaging performed early after ICI treatment, a transient increase in pancreatic volume may be observed prior to diabetes onset, possibly suggestive of an inflammatory process preceding diabetes presentation; however, at this stage, this data is only available for four patients [33,34]. A similar imaging phenomenon has been shown in immunotherapy-associated hypophysitis with transient pituitary enlargement followed by a progressive decrease in the size of the gland [35]. Given that imaging findings can be used for identifying pituitary as well as thyroid irAEs in subclinical disease, there may be a place for the use of imaging to complement biochemistry in the identification of ICI-DM in patients presenting with hyperglycaemia [36,37]. Serial abdominal imaging with a baseline comparator would be required to identify clinically meaningful changes.

4.3. Emerging Therapies

Given the irreversible nature of ICI-DM, commencement of lifelong insulin therapy is the mainstay of treatment. Current guidelines do not suggest the commencement of glucocorticoids nor immunomodulatory agents at disease onset [38]. Case reports of attempts to treat this irAE with corticosteroids have shown them to be futile in preserving β-cell function [39,40]. Corticosteroids are ineffective in T1DM and frequently precipitate hyperglycaemia [41]. Early immunomodulation has been shown to be beneficial in the treatment of certain irAEs, namely colitis, hepatitis, pneumonitis, arthritis, and possible for renal toxicity, however, not for any endocrinopathies [38]. Management of the metabolic derangements associated with ICI-DM should in general mimic those used to treat classic type 1 diabetes. This includes the emergency management of DKA if required [8]. The presence of other ICI-related endocrinopathies such as thyroid, pituitary and adrenal dysfunction should also be excluded [5].

Certain therapies may help to mitigate the exaggerated immune response and ultimately protect β-cells from damage induced by immune checkpoint inhibitor therapy. Preclinical studies have shown the reversal of autoimmune diabetes was possible using a JAK1 selective inhibitor, with up to 94% of newly diabetic mice remaining normoglycaemic while on treatment and 44% remaining so 60 days following drug discontinuation [42]. A further preclinical study in a mouse model suggests that if caught early, ICI-DM specifically could be reversed using a JAK1/JAK2 inhibitor to prevent T-cell proliferation in pancreatic islets while not affecting the antitumour effects of the ICI [43]. In this study, the JAK1/JAK2 inhibitor was administered prior to anti-PD-L1 therapy with diabetes development in 0/6 mice as opposed to 5/6 mice in the vehicle-treated group, with 4/6 mice remaining nondiabetic two weeks following treatment cessation. Similar results were seen in anti-PD-1-treated groups as well as in mice that received a repeat cycle of treatment. JAK1/JAK2 inhibition was also shown to reverse hyperglycaemia in 5/9 mice that were only administered the drug after diabetes diagnosis, with ongoing normal blood glucose levels even after stopping the treatment, suggesting that both protection against and reversal of ICI-DM may be possible. Similar robust protection against ICI-DM in mice using the JAK1/JAK2 inhibitor ruxolitinib was shown in a study that identified IL-21+ IFN-γ+ T follicular helper

cells as mediators of the condition, suggesting the mechanism of protection is through the blockade of the JAK-mediated IL-21 and IFN-γ signalling pathways [44]. ICI-DM is thought to be triggered by the activation of autoreactive T-cells that were being actively kept in check by the PD-1/PD-L1 interaction, compared with classical T1DM whereby T-cells are gradually "educated" to to attack pancreas [45]. Removing that interaction—especially on the PD-1-expressing CD4+ T follicular helper cells—results in the secretion of IL-21 and activation of CD8 T-cells that destroy the pancreatic reserve, usually in a matter of days [46]. Hence, there is interest in JAK inhibitors in ICI-DM, as they specifically block the signalling downstream of the IL-21 receptor, potentially cutting off the cascade before CD8+ cells are able to finish the job [44].

Emerging therapies in T1DM may be worth future consideration for translation to the ICI-DM setting (Table 3).

Table 3. Summary of potential ICI-DM therapies.

Therapy	Mechanism of Action	Current Status
Corticosteroids	Modulation of gene transcription via glucocorticoid receptor	No clinical benefit in ICI-DM. Frequently precipitate hyperglycaemia [39,40]
Baricitinib	JAK1/JAK2 inhibitor	Promising results in T1DM and preclinical ICI-DM studies [43]
Infliximab	Anti-TNF-α monoclonal antibody	Case reports of β-cell salvage in ICI-DM [47,48]
Teplizumab	Anti-CD3 monoclonal antibody	Not yet tested in ICI-DM, but FDA approved in T1DM [49]
Etanercept	TNF-α inhibitor	Not yet tested in ICI-DM, but promising clinical trial results in T1DM [50]
Golimumab	Anti-TNF-α monoclonal antibody	Not yet tested in ICI-DM, but promising clinical trial results in T1DM [51]

To date, the anti-CD3 monoclonal antibody Teplizumab is the only FDA-approved disease-modifying therapy in T1DM and is able to delay the progression of preclinical disease (stage 2) to clinical type 1 diabetes (stage 3) by a median of 32.5 months and preserve β-cell reserve [49]. Additional therapies targeting the TNF-α pathway have also shown promise. The TNF-α inhibitor etanercept has been shown in a phase 1 clinical trial to preserve a level of endogenous insulin production in newly diagnosed children with T1DM, with lower exogenous insulin requirement [50]. Additionally, the anti-TNF-α monoclonal antibody golimumab has demonstrated similar ability to maintain endogenous insulin production compared with placebo [51]. Recent evidence is also emerging that modulators of the JAK/STAT pathway have shown promise as therapies in the setting of T1DM. In humans, a phase 2 trial using baricitinib in newly diagnosed T1DM patients (BANDIT study) suggested a level of preservation of β-cell function was possible; the baricitinib-treated group at 48 weeks showed a higher mean c-peptide level (0.65 nmol/L vs. 0.43 nmol/L), as well as a lower mean daily insulin dose (0.41 U/kg vs. 0.52 U/kg) and lower mean HbA1c (53 mmol/mol (7.0%) vs. 58.5 mmol/mol (7.5%)) [52].

There is not yet a significant body of reports of immunomodulatory agents being used in ICI-DM; however, a case report has been published of ICI-DM being treated concurrently with a seronegative oligoarthritis using the anti-TNF-α therapy infliximab [42]. While it was suggested that the restoration of β-cell function occurred, the case described was atypical in its presentation with symptomatic hyperglycaemia 37 weeks following

ICI commencement, and the administration of intra-articular steroid injections was a possible confounding variable contributing to hyperglycaemia [48]. Following this, an additional two cases have recently been reported where infliximab was used to salvage β-cell function in newly hyperglycaemic ICI-treated patients, evidenced by the restoration and maintenance of c-peptide levels, which were detectable at diagnosis but low for paired blood glucose [47]. These cases were also atypical presentations; 118 and 39 weeks following ICI commencement, both autoantibody seronegative, and with pre-existing T2DM in the second patient. To date, there is little to no evidence for the use of infliximab in treating the fulminant subtype of ICI-DM presenting with DKA and undetectable c-peptide, warranting further research. In the future, a deeper understanding into the mechanism of ICI-DM should enable the development of targeted immunomodulation that prevents the condition while preserving the antitumour benefits of checkpoint blockade.

5. Conclusions

ICI-DM is a serious irAE associated with the use of PD-1/PD-L1 checkpoint inhibitors. It is a condition with a heterogenous presentation, most commonly occurring early after ICI commencement and usually with DKA; however, milder, more delayed, or subacute presentations are also seen. It can be characterised by autoimmune selective β-cell toxicity, evidenced by decreased c-peptide and permanent islet failure. Diagnosis can be supported with T1DM-associated autoantibodies and evidence of pancreatic atrophy on imaging, which may assist in delineating ICI-DM from other causes of hyperglycaemia.

Current focus is on the early diagnosis of ICI-DM and preventing progression to hyperglycaemic emergencies. Reversal of ICI-DM has not been achieved in humans thus far; however, preclinical models show that it may be possible with targeted immunomodulation, especially JAK1/JAK2 inhibition, as well as TNF-α/IFN-γ blockade. The challenge remains that ICI-DM is usually diagnosed after β-cell destruction is nearly complete. Future success will require predicting ICI-DM, early detection, and highly targeted immunomodulation without dampening the antitumour effects of the immunotherapy.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ICI	Immune Checkpoint Inhibitor
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death-Ligand 1
CTLA-4	Cytotoxic T Lymphocyte-Associated Antigen-4
irAE	Immune-Related Adverse Event
ICI-DM	Immune Checkpoint Inhibitor-Associated Diabetes
DKA	Diabetic Ketoacidosis

HLA	Human Leukocyte Antigen
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
HbA1c	Glycated Haemoglobin
PET	Positron Emission Tomography
SLE	Systemic Lupus Erythematosus
GAD	Glutamic Acid Decarboxylase
IA-2	Islet Antigen 2
ZnT8	Zinc Co-Transporter 8
CT	Computed Tomography
JAK	Janus Kinase
STAT	Signal Transducer and Activator of Transcription
IFN-γ	Interferon Gamma
TNF-α	Tumour Necrosis Factor Alpha
CD3	Cluster of Differentiation 3
CD4	Cluster of Differentiation 4
Th17	T helper 17
IL-21	Interleukin 21
FDA	Food and Drug Administration

Appendix A

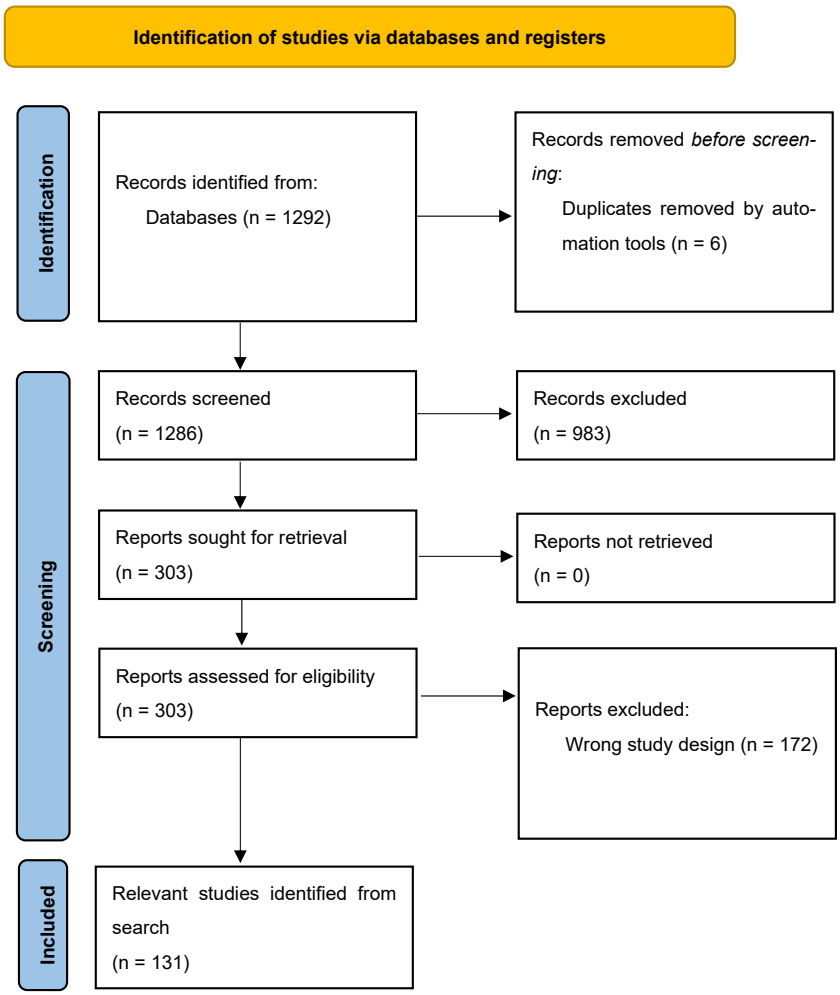

Figure A1. PRISMA flow diagram of study identification.

References

1. Shiravand, Y.; Khodadadi, F.; Kashani, S.M.A.; Hosseini-Fard, S.R.; Hosseini, S.; Sadeghirad, H.; Ladwa, R.; O'Byrne, K.; Kulasinghe, A. Immune Checkpoint Inhibitors in Cancer Therapy. *Curr. Oncol.* **2022**, *29*, 3044–3060. [CrossRef]
2. Yin, Q.; Wu, L.; Han, L.; Zheng, X.; Tong, R.; Li, L.; Bai, L.; Bian, Y. Immune-related adverse events of immune checkpoint inhibitors: A review. *Front. Immunol.* **2023**, *14*, 1167975. [CrossRef]
3. Wu, L.; Tsang, V.; Menzies, A.M.; Sasson, S.C.; Carlino, M.S.; Brown, D.A.; Clifton-Bligh, R.; Gunton, J.E. Risk Factors and Characteristics of Checkpoint Inhibitor-Associated Autoimmune Diabetes Mellitus (CIADM): A Systematic Review and Delineation from Type 1 Diabetes. *Diabetes Care* **2023**, *46*, 1292–1299. [CrossRef]
4. Wu, L.; Tsang, V.H.M.; Sasson, S.C.; Menzies, A.M.; Carlino, M.S.; Brown, D.A.; Clifton-Bligh, R.; Gunton, J.E. Unravelling Checkpoint Inhibitor Associated Autoimmune Diabetes: From Bench to Bedside. *Front. Endocrinol.* **2021**, *12*, 764138. [CrossRef]
5. Galligan, A.; Xu, W.; Fourlanos, S.; Nankervis, A.; Chiang, C.; Mant, A.M.; Parente, P.; Rischin, D.; Krishnamurthy, B.; Sandhu, S.; et al. Diabetes associated with immune checkpoint inhibition: Presentation and management challenges. *Diabet. Med.* **2018**, *35*, 1283–1290. [CrossRef]
6. Kyriacou, A.; Melson, E.; Chen, W.; Kempegowda, P. Is immune checkpoint inhibitor-associated diabetes the same as fulminant type 1 diabetes mellitus? *Clin. Med.* **2020**, *20*, 417–423. [CrossRef] [PubMed]
7. Byun, D.J.; Braunstein, R.; Flynn, J.; Zheng, J.; Lefkowitz, R.A.; Kanbour, S.; Girotra, M. Immune Checkpoint Inhibitor-Associated Diabetes: A Single-Institution Experience. *Diabetes Care* **2020**, *43*, 3106–3109. [CrossRef] [PubMed]
8. Akturk, H.K.; Kahramangil, D.; Sarwal, A.; Hoffecker, L.; Murad, M.H.; Michels, A.W. Immune checkpoint inhibitor-induced Type 1 diabetes: A systematic review and meta-analysis. *Diabet. Med.* **2019**, *36*, 1075–1081. [CrossRef] [PubMed]
9. Zhou, L.; Yang, S.; Li, Y.; Xue, C.; Wan, R. A comprehensive review of immune checkpoint inhibitor-related diabetes mellitus: Incidence, clinical features, management, and prognosis. *Front. Immunol.* **2024**, *15*, 1448728. [CrossRef]
10. Wu, L.; Carlino, M.S.; Brown, D.A.; Long, G.V.; Clifton-Bligh, R.; Mellor, R.; Moore, K.; Sasson, S.C.; Menzies, A.M.; Tsang, V.; et al. Checkpoint Inhibitor-Associated Autoimmune Diabetes Mellitus Is Characterized by C-peptide Loss and Pancreatic Atrophy. *J. Clin. Endocrinol. Metab.* **2024**, *109*, 1301–1307. [CrossRef]
11. Noble, J.A.; Valdes, A.M. Genetics of the HLA Region in the Prediction of Type 1 Diabetes. *Curr. Diabetes Rep.* **2011**, *11*, 533–542. [CrossRef]
12. Barroso-Sousa, R.; Barry, W.T.; Garrido-Castro, A.C.; Hodi, F.S.; Min, L.; Krop, I.E.; Tolaney, S.M. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. *JAMA Oncol.* **2018**, *4*, 173–182. [CrossRef]
13. Tsang, V.H.M.; McGrath, R.T.; Clifton-Bligh, R.J.; A Scolyer, R.; Jakrot, V.; Guminski, A.D.; Long, G.V.; Menzies, A.M. Checkpoint Inhibitor-Associated Autoimmune Diabetes Is Distinct from Type 1 Diabetes. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 5499–5506. [CrossRef] [PubMed]
14. Stamatouli, A.M.; Quandt, Z.; Perdigoto, A.L.; Clark, P.L.; Kluger, H.; Weiss, S.A.; Gettinger, S.; Sznol, M.; Young, A.; Rushakoff, R.; et al. Collateral Damage: Insulin-Dependent Diabetes Induced with Checkpoint Inhibitors. *Diabetes* **2018**, *67*, 1471–1480. [CrossRef]
15. Kotwal, A.; Haddox, C.; Block, M.; Kudva, Y.C. Immune checkpoint inhibitors: An emerging cause of insulin-dependent diabetes. *BMJ Open Diabetes Res. Care* **2019**, *7*, e000591. [CrossRef]
16. De Filette, J.M.K.; Pen, J.J.; Decoster, L.; Vissers, T.; Bravenboer, B.; Van der Auwera, B.J.; Gorus, F.K.; O Roep, B.; Aspeslagh, S.; Neyns, B.; et al. Immune checkpoint inhibitors and type 1 diabetes mellitus: A case report and systematic review. *Eur. J. Endocrinol.* **2019**, *181*, 363–374. [CrossRef] [PubMed]
17. Hazime, R.; Lamjadli, S.; Guennouni, M.; Belkrachni, M.; Eddehbi, F.-E.; Oujamaa, I.; Elmoumou, L.; Bourrahouate, A.; Sab, I.A.; Baizri, H.; et al. Autoantibodies in type 1 diabetes: Prevalence and clinical profiles. *Diabetes Epidemiol. Manag.* **2025**, *17*, 100246. [CrossRef]
18. Williams, C.L.; Fareed, R.; Mortimer, G.L.M.; Aitken, R.J.; Wilson, I.V.; George, G.; Gillespie, K.M.; Williams, A.J.K.; The BOX Study Group; Ballav, C.; et al. The longitudinal loss of islet autoantibody responses from diagnosis of type 1 diabetes occurs progressively over follow-up and is determined by low autoantibody titres, early-onset, and genetic variants. *Clin. Exp. Immunol.* **2022**, *210*, 151–162. [CrossRef]
19. Bingley, P.J. Clinical Applications of Diabetes Antibody Testing. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 25–33. [CrossRef] [PubMed]
20. Lo Preiato, V.; Salvagni, S.; Ricci, C.; Ardizzoni, A.; Pagotto, U.; Pelusi, C. Diabetes mellitus induced by immune checkpoint inhibitors: Type 1 diabetes variant or new clinical entity? Review of the literature. *Rev. Endocr. Metab. Disord.* **2021**, *22*, 337–349. [CrossRef]
21. McGrail, C.; Chiou, J.; Elgamal, R.; Luckett, A.M.; Oram, R.A.; Benaglio, P.; Gaulton, K.J. Genetic Discovery and Risk Prediction for Type 1 Diabetes in Individuals Without High-Risk HLA-DR3/DR4 Haplotypes. *Diabetes Care* **2025**, *48*, 202–211. [CrossRef]

22. Yamazaki, N.; Kiyohara, Y.; Uhara, H.; Fukushima, S.; Uchi, H.; Shibagaki, N.; Tsutsumida, A.; Yoshikawa, S.; Okuyama, R.; Ito, Y.; et al. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. *Cancer Chemother. Pharmacol.* **2015**, *76*, 997–1004. [CrossRef]
23. Wright, J.J.; Salem, J.-E.; Johnson, D.B.; Lebrun-Vignes, B.; Stamatouli, A.; Thomas, J.W.; Herold, K.C.; Moslehi, J.; Powers, A.C. Increased Reporting of Immune Checkpoint Inhibitor–Associated Diabetes. *Diabetes Care* **2018**, *41*, e150–e151. [CrossRef] [PubMed]
24. Liu, J.; Zhou, H.; Zhang, Y.; Fang, W.; Yang, Y.; Huang, Y.; Zhang, L. Reporting of Immune Checkpoint Inhibitor Therapy-Associated Diabetes, 2015–2019. *Diabetes Care* **2020**, *43*, e79–e80. [CrossRef]
25. Zhan, M.; Long, Q.; He, J.; Huang, L.; Wu, B.; Xu, H.; Mo, L.; Xu, T. Immune checkpoint inhibitor-induced diabetes mellitus: Clinical characteristics and risk factors. *Front. Immunol.* **2025**, *16*, 1499074. [CrossRef]
26. Wu, L.; Tsang, V.; Clifton-Bligh, R.; Carlino, M.S.; Tse, T.; Huang, Y.; Oatley, M.; Cheung, N.W.; Long, G.V.; Menzies, A.M.; et al. Hyperglycemia in patients treated with immune checkpoint inhibitors: Key clinical challenges and multidisciplinary consensus recommendations. *J. Immunother. Cancer* **2025**, *13*, e011271. [CrossRef] [PubMed]
27. Zhang, A.L.; Wang, F.; Chang, L.S.; McDonnell, M.E.; Min, L. Coexistence of Immune Checkpoint Inhibitor-Induced Autoimmune Diabetes and Pancreatitis. *Front. Endocrinol.* **2021**, *12*, 620522. [CrossRef]
28. Quandt, Z.; Perdigoto, A.; Anderson, M.S.; Herold, K.C. Checkpoint Inhibitor-Induced Autoimmune Diabetes: An Autoinflammatory Disease. *Cold Spring Harb. Perspect. Med.* **2025**, *15*, a041603. [CrossRef]
29. Perdigoto, A.L.; Quandt, Z.; Anderson, M.; Herold, K.C. Checkpoint inhibitor-induced insulin-dependent diabetes: An emerging syndrome. *Lancet Diabetes Endocrinol.* **2019**, *7*, 421–423. [CrossRef] [PubMed]
30. Akturk, H.K.; Michel, K.; Couts, K.; Karakus, K.E.; Robinson, W.; Michels, A. Routine Blood Glucose Monitoring Does Not Predict Onset of Immune Checkpoint Inhibitor–Induced Type 1 Diabetes. *Diabetes Care* **2024**, *47*, e29–e30. [CrossRef]
31. Wu, L.; Wentworth, J.M.; Liddle, C.; Fewings, N.; Carlino, M.; Brown, D.A.; Clifton-Bligh, R.; Long, G.V.; Scolyer, R.A.; Norris, N.; et al. Pancreatic volume and immune biomarkers predict checkpoint inhibitor-associated autoimmune diabetes in humans. *J. Clin. Investig.* **2025**, *136*, e192938. [CrossRef] [PubMed]
32. Virostko, J.; Williams, J.; Hilmes, M.; Bowman, C.; Wright, J.J.; Du, L.; Kang, H.; Russell, W.E.; Powers, A.C.; Moore, D.J. Pancreas Volume Declines During the First Year After Diagnosis of Type 1 Diabetes and Exhibits Altered Diffusion at Disease Onset. *Diabetes Care* **2019**, *42*, 248–257. [CrossRef]
33. Marchand, L.; Thivolet, A.; Dalle, S.; Chikh, K.; Reffet, S.; Vouillarmet, J.; Fabien, N.; Cugnet-Anceau, C.; Thivolet, C. Diabetes mellitus induced by PD-1 and PD-L1 inhibitors: Description of pancreatic endocrine and exocrine phenotype. *Acta Diabetol.* **2019**, *56*, 441–448. [CrossRef]
34. Wei, H.-H.; Lai, Y.-C.; Lin, G.; Lin, C.-W.; Chang, Y.-C.; Chang, J.W.-C.; Liou, M.-J.; Chen, I.-W. Distinct changes to pancreatic volume rather than pancreatic autoantibody positivity: Insights into immune checkpoint inhibitors induced diabetes mellitus. *Diabetol. Metab. Syndr.* **2024**, *16*, 26. [CrossRef]
35. Lasocki, A.; Iravani, A.; Galligan, A. The imaging of immunotherapy-related hypophysitis and other pituitary lesions in oncology patients. *Clin. Radiol.* **2021**, *76*, 325–332. [CrossRef]
36. Galligan, A.; Iravani, A.; Lasocki, A.; Wallace, R.; Weppler, A.M.; Sachithanandan, N.; Chiang, C.; Colman, P.G.; Wentworth, J.; Spain, L.; et al. Imaging for assessment of cancer treatment response to immune checkpoint inhibitors can be complementary in identifying hypophysitis. *Front. Endocrinol.* **2023**, *14*, 1295865. [CrossRef]
37. Galligan, A.; Wallace, R.; Krishnamurthy, B.; Kay, T.W.H.; Sachithanandan, N.; Chiang, C.; Sandhu, S.; Hicks, R.J.; Iravani, A. Increased Thyroidal Activity on Routine FDG-PET/CT after Combination Immune Checkpoint Inhibition: Temporal Associations with Clinical and Biochemical Thyroiditis. *Cancers* **2023**, *15*, 5803. [CrossRef]
38. Haanen, J.; Obeid, M.; Spain, L.; Carbonnel, F.; Wang, Y.; Robert, C.; Lyon, A.; Wick, W.; Kostine, M.; Peters, S.; et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* **2022**, *33*, 1217–1238. [CrossRef]
39. Daetwyler, E.; Zippelius, A.; Danioth, S.; Donath, M.Y.; Gut, L. Nivolumab-induced diabetes mellitus—A case report with literature review of the treatment options. *Front. Immunol.* **2023**, *14*, 1248919. [CrossRef] [PubMed]
40. Aleksova, J.; Lau, P.K.; Soldatos, G.; McArthur, G. Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma. *BMJ Case Rep.* **2016**, *2016*, bcr2016217454. [CrossRef] [PubMed]
41. Katz, A.; Shulkin, A.; Housni, A.; Roy-Fleming, A.; Rabasa-Lhoret, R.; Yale, J.; Tsoukas, M.A.; Peters, T.M.; Brazeau, A. A systematic review of glucocorticoid use in type 1 diabetes: Glycaemic effects and clinical management strategies. *Diabetes Obes. Metab.* **2026**, *28*, 2594–2614. [CrossRef]
42. Trinh, B.; Donath, M.Y.; Läubli, H. Successful Treatment of Immune Checkpoint Inhibitor–Induced Diabetes with Infliximab. *Diabetes Care* **2019**, *42*, e153–e154. [CrossRef]

43. Ge, T.; Phung, A.; Jhala, G.; Trivedi, P.; Principe, N.; De George, D.J.; Pappas, E.G.; Litwak, S.; Sanz-Villanueva, L.; Catterall, T.; et al. Diabetes induced by checkpoint inhibition in nonobese diabetic mice can be prevented or reversed by a JAK1/JAK2 inhibitor. *Clin. Transl. Immunol.* **2022**, *11*, e1425. [CrossRef] [PubMed]
44. Ge, T.; Jhala, G.; Fynch, S.; Akazawa, S.; Litwak, S.; Pappas, E.G.; Catterall, T.; Vakil, I.; Long, A.J.; Olson, L.M.; et al. The JAK1 Selective Inhibitor ABT 317 Blocks Signaling Through Interferon-gamma and Common gamma Chain Cytokine Receptors to Reverse Autoimmune Diabetes in NOD Mice. *Front. Immunol.* **2020**, *11*, 588543. [CrossRef]
45. Youssef, N.; Noureldein, M.; Daoud, G.; Eid, A.A. Immune checkpoint inhibitors and diabetes: Mechanisms and predictors. *Diabetes Metab.* **2021**, *47*, 101193. [CrossRef]
46. Huang, N.L.; Ortega, J.G.; Kimbrell, K.; Lee, J.; Scott, L.N.; Peluso, E.M.; Wang, S.J.; Kao, E.Y.; Kim, K.; Olay, J.; et al. Polyfunctional T follicular helper cells drive checkpoint-inhibitor diabetes and are targeted by JAK inhibitor therapy. *J. Clin. Investig.* **2025**, *10*, e188843. [CrossRef] [PubMed]
47. Savion Gaiger, N.; Hurwitz, M.E.; Hafez, N.; Kluger, H.M.; Herold, K.C.; Perdigoto, A.L. Immune checkpoint inhibitor-induced diabetes can potentially be effectively treated with infliximab: A case report of two patients. *Front. Endocrinol.* **2025**, *16*, 1697724. [CrossRef]
48. Galligan, A.; Krishnamurthy, B.; Kay, T.W. Comment on Trinh et al. Successful Treatment of Immune Checkpoint Inhibitor–Induced Diabetes with Infliximab. *Diabetes Care* **2020**, *43*, e10. [CrossRef]
49. Ramos, E.L.; Dayan, C.M.; Chatenoud, L.; Sumnik, Z.; Simmons, K.M.; Szypowska, A.; Gitelman, S.E.; A Knecht, L.; Niemoeller, E.; Tian, W.; et al. Teplizumab and beta-Cell Function in Newly Diagnosed Type 1 Diabetes. *N. Engl. J. Med.* **2023**, *389*, 2151–2161. [CrossRef]
50. Mastrandrea, L.; Yu, J.; Behrens, T.; Buchlis, J.; Albini, C.; Fourtner, S.; Quattrin, T. Etanercept Treatment in Children with New-Onset Type 1 Diabetes. *Diabetes Care* **2009**, *32*, 1244–1249. [CrossRef] [PubMed]
51. Quattrin, T.; Haller, M.J.; Steck, A.K.; Felner, E.I.; Li, Y.; Xia, Y.; Leu, J.H.; Zoka, R.; Hedrick, J.A.; Rigby, M.R.; et al. Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. *N. Engl. J. Med.* **2020**, *383*, 2007–2017. [CrossRef] [PubMed]
52. Waibel, M.; Wentworth, J.M.; So, M.; Couper, J.J.; Cameron, F.J.; MacIsaac, R.J.; Atlas, G.; Gorelik, A.; Litwak, S.; Sanz-Villanueva, L.; et al. Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes. *N. Engl. J. Med.* **2023**, *389*, 2140–2150. [CrossRef] [PubMed]