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REVIEW ARTICLE

The multifaceted nature of diabetes mellitus induced by checkpoint inhibitors

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Abstract

Immune checkpoint inhibitors (CPI) are increasingly being used in oncology, and many autoimmune side effects have been described. Diabetes mellitus (DM) has been reported in approximately 1% of subjects treated with programmed cell death-1 and programmed death ligand 1 (PD-1/PD-L1) inhibitors, alone or in association with CTLA-4 inhibitors. In the present mini-review, we aimed to describe different clinical pictures and pathophysiology associated with these forms of diabetes. Data on CPI-related DM was gathered from the largest case series in the literature and from our centre dedicated to immunotherapy complications (ImmuCare—Hospices Civils de Lyon). Most cases are acute autoimmune insulin-dependent diabetes which are similar to fulminant diabetes (extremely acute onset with concomitant near-normal HbA1c levels). Other cases, however, have a phenotype close to type 2 diabetes or appear as a decompensation of previously known type 2 diabetes. The occurrence of diabetes can also be a complication of autoimmune pancreatitis induced by CPI use. Finally, two cases of diabetes in a context of autoimmune lipoatrophy have recently been described. Regarding the wide variety of CPI-induced diabetes, the discovery of a glucose disorder under CPI should motivate specialised care for aetiological diagnosis and appropriate treatment.

Keywords Diabetes mellitus · Fulminant diabetes · Autoimmune diabetes · Immune checkpoint inhibitors side effects · Immunotherapy · Programmed cell death-1 (PD-1) · Anti-PD-1 · Programmed death ligand 1 (PD-L1) · Anti-PD-L1 · Pancreas volume · Beta cell pancreatic function · Alpha cell pancreatic function · Exocrine pancreatic function · Autoimmune pancreatitis · Autoimmune generalised lipoatrophy · Autoimmune lipodystrophy

Abbreviations

AGL	Autoimmune generalised lipodystrophy
BMI	Body mass index
CPI	Checkpoint inhibitors
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DM	Diabetes mellitus
FD	Fulminant diabetes
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
NASH	Non-alcoholic steatohepatitis

Introduction

Immune checkpoints are regulatory molecules that modulate T cell stimulation or inhibition, thereby preventing inadequate responses and promoting self-tolerance. Immune checkpoint inhibitors (CPI) are increasingly being used in oncology to treat solid tumours. This new therapeutic class

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includes programmed death 1 (PD-1) antibodies (nivolumab and pembrolizumab), programmed death ligand 1 (PD-L1) antibodies (atezolizumab, avelumab, and durvalumab), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies (ipilimumab and tremelimumab). These antibodies, which activate tumour-reactive T cells, have also been associated with many immune-related adverse events [1].

In parallel, different immunotherapies have shown promise in rodent models to treat autoimmune diabetes and have been tested in humans to try to halt or to delay destruction of β-cells in autoimmune type 1 diabetes, including CTLA-4 immunoglobulins [2]. These last agents have been successful in reverting autoimmune diabetes in animal models in combination with other immunosuppressive treatments, and abatacept (CTLA-4 immunoglobulin fusion protein) effectively delayed loss of β-cell in a phase 3 study with recent-onset type 1 diabetes subjects [3]. On the contrary, mice with loss of CTLA-4 develop massive tissue infiltration by self-reactive T cells [4].

Preclinical studies in rodents have shown a key role of PD1 in the development of type 1 diabetes [5–7], and overexpression/pharmacological restoration of PD-L1 in non-obese diabetic mice can reverse autoimmune diabetes [8]. In human studies, PD-1 mRNA expression in $CD4^+$ T cells has been shown to be significantly lower in patients with autoimmune type 1 diabetes than in healthy control subjects [9]. These results indicate that a low PD-1 expression in $CD4^+$ T cells, as well as the pharmacological blockade of PD-1, might contribute to the development of autoimmune type 1 diabetes through T cell activation directed towards beta cells. These results suggest that CTLA-4 and PD-1/PD-L1 pathways have a major role in the regulation of beta cells tolerance.

According to Stamatouli et al. [10], in the largest well-described case series (27 cases) published thus far, the incidence of CPI-related diabetes mellitus (DM) could come close to 1% in subjects treated with anti-PD-1 or anti-PD-L1 antibodies, alone or in association with anti-CTLA-4 antibodies. Most of these cases are similar to fulminant diabetes (FD), with an extremely acute onset (frequent ketoacidosis) and a near-normal HbA1c.

A recent study that analysed databases of individual case safety reports between 2014 and 2018, reported 283 cases of new-onset diabetes under CPI [11]. It is of note that, in this case series, 12 subjects developed diabetes under anti-CTLA-4 antibodies alone, but the association between anti-CLTA-4 and autoimmune diabetes, undescribed so far, remains to be confirmed. It also remains to determine if the addition of CTLA-4 antibodies with PD-1/PD-L1 antibodies could worsen the risk to develop diabetes mellitus.

Beside these cases of acute autoimmune diabetes, clinical presentation and pathophysiology of diabetes mellitus induced by CPI can vary and be misleading. In the present mini-review, data on CPI-related DM were gathered from the largest case series in the literature and from our centre dedicated to immunotherapy complications (ImmuCare—Hospices Civils de Lyon). This was done with the aim to describe different clinical and biological profiles of CPI-induced diabetes and their potential pathophysiology. Acute diabetes with autoimmune destruction of beta cells, diabetes induced by autoimmune pancreatitis, type 2 diabetes-like phenotypes, and diabetes following autoimmune lipoatrophy are the main pathophysiological features of CPI-induced DM reported at the present time (Fig. 1). Key distinguishing features, pathophysiological mechanisms, and adequate treatments of various CPI-induced DM are summarised in Table 1.

Acute autoimmune insulin-dependent diabetes

Acute autoimmune insulin-dependent DM is the most described form of diabetes induced by CPI, and many case reports and case series on this condition are now available in the literature. This form of DM shares many similarities with FD, which is rarely found in Caucasian populations. FD was first described in East Asian subjects and was characterised by an extremely acute onset of diabetes, often associated with a clinical presentation of ketoacidosis, and concomitant near-normal HbA1c levels [12]. In the paper by Stamatouli et al., 27 cases (17 men and 10 women) of CPI-induced autoimmune diabetes were described [10]. Mean age at onset was 66 years. Mean body mass index (BMI) was 26 kg/m^2. Median time of onset was 20 weeks after CPI initiation (anti-PD-1/PD-L1 antibodies alone or in association with anti-CTLA-4). In other cases, however, occurrence of CPI-related DM has been reported to range between 1 week and 12 months after treatment initiation [13, 14]. In the Stamatouli et al. study, in 60% of cases, the clinical presentation is a ketoacidosis. The mean HbA1c at onset was 63 mmol/mol (7.95%) indicating a short duration of hyperglycaemia. C-peptide was low or undetectable at the time of diagnosis in 85% of cases. Forty per cent of subjects presented at least one auto-antibody related to type 1 diabetes. HLA typing revealed a predominance of HLA DR4 (76%). Seventy per cent of patients exhibited another autoimmune side effect of CPI. It is noteworthy that 6 patients from this case series exhibited either type 2 diabetes ($n=2$) or pre-diabetes ($n=4$), but whether or not their phenotypes are similar to the cases described in the following section of the present review is unknown.

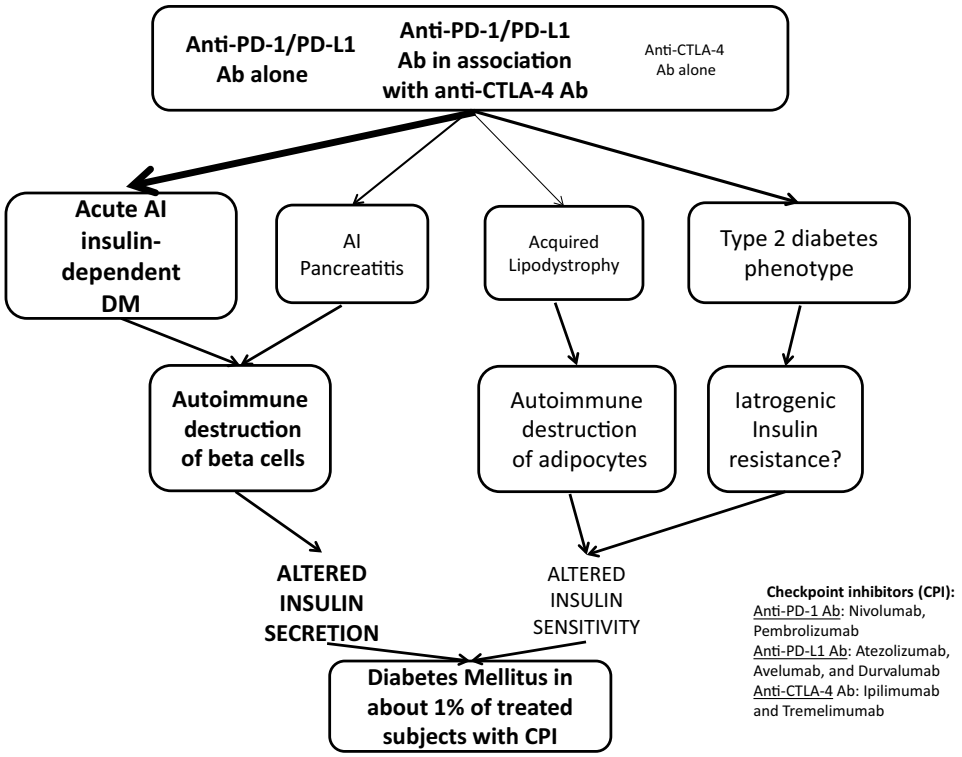

Fig. 1 Different forms of diabetes mellitus induced by checkpoint inhibitors. *Ab* antibodies, *AI* autoimmune, *DM* diabetes mellitus, *CPI* checkpoint inhibitors, *PD-1* programmed death 1, *PD-L1* programmed death ligand 1, *CTLA-4* cytotoxic T-lymphocyte antigen 4

In such cases of CPI-induced FD, the prevalence of pre-existing islet auto-antibodies versus seroconversion after the initiation of CPI therapy remains unknown [15, 16].

Blockade of PD-1 or PD-L1 could be the cause of a brutal and major activation of $CD8^+$ T cell clones directed towards beta cells, leading to acute and severe beta cell destruction and DM. Indeed, our team previously reported the case of 4 subjects with CPI-induced FD who exhibited a completely abolished C-peptide response to a mixed-meal tolerance test performed only 1 month after DM diagnosis and despite the use of an ultrasensitive assay [17]. This C-peptide response differs from that generally observed during the first year of a classical type 1 diabetes [18].

The possible involvement of pancreatitis in these fulminant forms of diabetes is still under debate. Indeed, in the case series reported by Stamatouli [10], 42% of subjects had evidence of pancreatitis at the time of DM onset (i.e. increased plasma lipase levels and/or pancreatic oedema). In 4 subjects, random glucagon levels were not reduced, and the authors concluded that alpha cells were not affected [10]. Our team, however, has reported the case of a Caucasian man with pulmonary pleomorphic carcinoma, treated with PD-1 inhibitor, who developed FD with bi-hormonal endocrine pancreatic failure, decrease in exocrine pancreatic function without abdominal pain or steatorrhoea, and pancreas atrophy after an initial 15% increase in pancreatic volume [19]. In addition, a second CPI-induced FD patient from our case series demonstrated a blunted glucagon response [19]. However, an 18F-FDG PET/CT, performed 1 week before diabetes onset, did not show pancreatic hypermetabolism unlike what is usually observed in autoimmune pancreatitis. Thus, in CPI-induced autoimmune diabetes, features of associated pancreatitis differ from that of autoimmune pancreatitis and need to be explored more carefully.

A rescue therapy using glucocorticoids, or other immune interventions, initiated after onset, would be useless in the case of major beta cell destruction. Indeed, 4 attempts of CPI-related DM reversion using systemic corticosteroids have been reported without success [16, 20–22]. Contrary to other immune-related adverse events, there is currently no specific treatment for CPI-induced autoimmune DM. Thus, after the onset of CPI-related FD, insulin therapy is needed and discontinuation of CPI is not required. CPI-induced FD cases were immediately treated with intensive and definitive insulinotherapy. Some difficulties in achieving correct metabolic control are reported, due to high glucose variability [23, 24]. This early high glucose variability can be a consequence of the pathophysiological features of CPI-induced FD including blunted glucagon response and abolished C-peptide response to stimulation. The simultaneous presence of corticotroph deficiency, another autoimmune adverse effect of CPI, could also lead to this high glucose variability [25].

Table 1 Key distinguishing features, pathophysiology mechanisms, and adequate treatments for different forms of diabetes mellitus induced by checkpoint inhibitors

	Acute autoimmune insulin-dependent diabetes	Phenotype of type 2 diabetes/decompensation of type 2 diabetes	Autoimmune pancreatitis	Autoimmune lipoatrophy
Key distinguishing features	Ketoacidosis (50%) or severe acute cardinal syndrome Near-normal HbA1c Possible increase in lipase level Undetectable C-peptide Positivity of type 1 diabetes auto-antibodies in about half of cases HLA-DR4	Increased BMI Metabolic comorbidities Medical history of type 2 diabetes High HbA1c level Detectable C-peptide	Exocrine insufficiency (steatorrhoea; decrease in faecal elastase-1) Detectable C-peptide at early stage Increase in lipase level 18FDG PET TDM: hypermetabolism of the pancreas Pancreatitis may be asymptomatic	Clinical lipoatrophy Severe Insulin resistance NASH Hypertriglyceridaemia Detectable C-peptide Low or undetectable level of leptin and adiponectin
Pathophysiology	*Insulinopaenia* Beta cell death after sudden and major activation of beta cell-reactive $CD8^+$ T cell clones Associated pancreatitis?	*Insulin resistance* Inflammation induced by $CD8^+$ T cells and tumour lysis? *Insulinopaenia?* Reduction in beta cell mass/function?	*Insulinopaenia* Destruction of both exocrine and endocrine pancreatic tissue resulting in beta cell deficiency	*Insulin resistance* Inability to store lipids in adipocytes (immune-mediated destruction of adipocytes) induces ectopic fat deposits
Adequate treatment	Immediate and definitive intensive insulin therapy	Metformin, transitory (or definitive) insulin therapy Interest of GLP1-agonist and i-SGLT2?	Basal insulin + sulfonylurea in early stage; then intensive insulin therapy if necessary	Metformin, glitazone (if available) and intensive insulin therapy Leptin replacement therapy?

BMI body mass index, *NASH* non-alcoholic steatohepatitis

Clinical presentation of type 2 diabetes

As previously mentioned, in the series of Stamatouli et al. [10], 6 subjects exhibited either previous type 2 DM or pre-diabetes before CPI initiation, indicating that CPI could also decompensate glucose control. In our case series of CPI-related DM [17], 2 subjects exhibited a clinical presentation different from those with FD diabetes. They had a higher BMI (both 26 kg/m^2), were older (72 and 83 years vs. 55–69 years for FD subjects), and had a history of hypertension. They did not present ketoacidosis, C-peptide was detectable, and HbA1c was higher at onset [17]. A recent paper reported 9 cases of pre-existing type 2 diabetes worsening during CPI therapy [26]. The impact of anti-PD-1 treatments on blood glucose levels has been analysed in the study by Magis et al. [27], and a slight trend for glycaemic increase was noted for subjects with pre-existing type 2 diabetes ($n = 47$) [27]. Furthermore, it has also been shown that CPI treatments induce HbA1c increase in non-diabetic subjects [28]. In light of these converging data, it can be postulated that CPI has detrimental effects on glucose metabolism.

The pathophysiology remains largely uncertain, but it is possible that the inflammation induced by cytotoxic lymphocytes and tumour lysis could lead to insulin resistance. However, the question of CPI-induced reduction in beta cell mass should also be discussed. Indeed, in our case series, a decrease in pancreas volume was observed during the follow-up of 2 subjects with a phenotype close to type 2 DM.

Ideal treatment, in this context, should include insulin sensitiser (metformin or glitazone) with or without temporary or permanent insulinotherapy. The added value of GLP1 Receptor Agonist (GLP-1RA) and/or SGLT2 inhibitors should be discussed. One subject from our case series stopped insulin therapy 3 months after onset and was still free from anti-diabetic drugs 1 year after anti-PD-1/PD-L1 treatment withdrawal.

Complication of autoimmune pancreatitis

Autoimmune pancreatitis is a rare side effect of cancer immunotherapy [1]. A recent case of insulin-dependent diabetes following autoimmune pancreatitis has been reported by Larger's team [29]. A 63-year-old Caucasian subject treated with PD-1 inhibitor (nivolumab) presented a localised 18F-FDG uptake by the pancreatic tail (after 15 months of treatment), associated with a fatty peripancreatic infiltration on the CT scan. He was asymptomatic, and lipase level was normal. Three months later, fasting glycaemia was 11 mmol/L [78 mmol/mol (HbA1c 9.3%)]. Auto-antibodies were negative. Fasting C-peptide remained detectable at 0.41 nmol/L (normal range 0.27–1.27 nmol/L). Blood lipase was threefold above normal, and faecal elastase-1 was decreased at 58 mg/g (normal values > 200). MRI showed a 50% decrease in the initial pancreatic volume. Basal insulin therapy, metformin, and sulfonylurea were initiated. Rapidly, the patient presented profuse diarrhoea revealing exogenous pancreatic insufficiency (faecal elastase-1 < 15 mg/g), and the C peptide response worsened (0.10 nmol/L in basal state and 0.50 nmol/L 2-h after mixed-meal tolerance test) leading to pancreatic enzyme replacement and basal-bolus insulin regimen treatment.

We present herein another case of a 69-year-old woman treated for metastatic melanoma using a combination of nivolumab and intratumoural ipilimumab. After 6 months of treatment, a symptomatic acute pancreatitis was diagnosed based on the increase in lipase value to 287 UI/L (normal range < 60). The MRI revealed a moderate oedema of the pancreatic gland, and the 18F-FDG PET imaging showed an inflammatory reaction of pancreatic tissues. Accordingly, CPI therapy was discontinued. Exhaustive aetiologic investigation for this acute pancreatitis remained negative. A second episode of acute pancreatitis occurred 5 months later (serum lipases = 1236 UI/L). Blood glucose was 124 mg/dL (6.82 mmol/L), and HbA1c level was 48 mmol/mol (6.5%). Antibodies related to type 1 diabetes were negative. The patient had no personal or family history of DM, and her BMI was in the normal range. Glucocorticoid and/or immunosuppressive treatment were under discussion when finally a spontaneous improvement in this CPI-related DM was observed.

Abu-Sbeih et al. described the characteristics of pancreatic injury induced by CPI among 2279 patients. They reported 82 (4%) pancreatic injuries with only 32 patients exhibiting typical pancreatitis. Among these 82 patients with CPI-induced pancreatic injury, 6 developed DM (5/6 treated by insulin).

In this context, the pathophysiology of DM is the destruction of both exocrine and endocrine pancreatic tissues resulting in beta cell deficiency. Thus, the adequate treatment is usually intensive insulin therapy. In some cases, however, depending on the residual beta cell mass, treatment combining basal insulin, and oral secretagogues can maintain correct metabolic control. The use of GLP1-RA is theoretically contraindicated.

Autoimmune lipoatrophy

Two exceptional cases of diabetes onset in a context of autoimmune generalised lipodystrophy (AGL) induced by anti-PD1 agent (nivolumab) were recently described. AGL

is a rare autoimmune disease characterised by the loss of subcutaneous adipose tissue. This leads to severe insulin resistance with diabetes mellitus, hypertriglyceridaemia, and non-alcoholic steatohepatitis. This syndrome is associated with autoimmune diseases in 25% of the cases.

First, a 57-year-old woman with a metastatic renal carcinoma and a medical history of type 2 diabetes was treated with 16 doses of nivolumab (second line after pazopanib) [30]. Two months after the initiation of nivolumab therapy, lipoatrophy appeared in the face, neck, shoulders, arms, and buttocks. Simultaneously, her diabetes control worsened, requiring maximum doses of metformin and pioglitazone associated with 1.5 units/kg/day of insulin. Triglycerides level was high (344 mg/dL). Glycaemic control improved after the withdrawal of nivolumab. A subcutaneous biopsy demonstrated chronic lobular panniculitis (lymphoplasmocytic with mast cells) with extensive fibro-elastotic replacement [30]. However, a normal pattern of adipose tissue was observed in her abdomen and calves, and leptin level was still detectable at 8.5 ng/dL (reference values: 8–38.9 ng/dL), contrary to the typical clinico-biological presentation of AGL.

Our team also reported a case of AGL in a 62-year-old Caucasian woman, with metastatic melanoma [31]. After 18 months of nivolumab treatment (34 courses), she rapidly developed severe weight loss, major nonketotic hyperglycaemia (24.9 mmol/L and HbA1c 101 mmol/mol (11.4%), hypertriglyceridaemia (563 mg/dL), and non-alcoholic steatohepatitis (NASH). Clinical examination found severe generalised subcutaneous fat atrophy, with acanthosis nigricans. Changes in physical appearance lasted a few months. Plasma leptin became undetectable, and there was a strong decrease in plasma adiponectin level. Diabetes was associated with severe insulin resistance, requiring a high-dose basal-bolus insulin regimen (1.6 U/kg/d) in association with metformin. Subcutaneous biopsy found that atrophic adipose tissue was extensively infiltrated with cytotoxic $CD8^+$ T lymphocytes and the presence of fibrosis.

Pathophysiology of this condition is marked by severe insulin resistance due to the inability of adipocytes to store lipids which in turn leads to multiple ectopic lipid deposits. As mentioned in the two cases, the treatment should include insulin sensitiser (metformin and/or glitazone) and insulin. Leptin replacement therapy needs to be evaluated.

Conclusion

In the present mini-review, we describe the multifaceted nature of diabetes mellitus induced by CPI. Accessing up-to-date information about different clinical phenotypes and pathophysiologies of various forms of CPI-related DM is required to propose adequate treatment. Besides the fulminant nature of acute autoimmune insulin-dependent diabetes, characterised by predominant insulinopaenia, several other clinical presentations of CPI-induced DM onset are reported. Diabetes following post-pancreatitis endocrine pancreas insufficiency is distinguishable due to the role played by insulinopaenia which is usually associated with exocrine pancreas insufficiency. Some aetiologies of CPI-induced DM are characterised by insulin resistance: new onset of DM phenotypes close to type 2 diabetes, hyperglycaemic decompensation of a previous state of insulin resistance, or induction of severe insulin resistance in the case of autoimmune lipodystrophy.

Regarding the wide variety of CPI-induced diabetes, the discovery of a glucose disorder under CPI should motivate specialised care for aetiological diagnosis and appropriate treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no duality of interest associated with this manuscript.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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