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Acute diabetes complications

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1. RECOMMENDATIONS

General (intended to prevent or to limit the risk of acute complications)

A. Diabetic status should be verified during Comprehensive Geriatric Assessment, to assess whether the patient has an existing DM diagnosis or there is sufficient reason to suspect that a diagnosis is needed.
B. Drug therapy should be evaluated, looking for potentially diabetogenic or hypoglycemic drugs, to define their risks and benefits.
C. In presence of an acute event of any type, glycemia should be checked. In patients with an established diagnosis of DM, measurement of ketonemia/ketonuria is mandatory.
D. In geriatric patients, management of glycemic control, measured with HbA1c levels, should be personalized according to the patient's general health status, comorbidities, and life expectancy.
E. Patients, family members, and caregivers must be fully educated on both prevention and early recognition of acute diabetes complications.
F. First-generation glucose lowering drugs, such as sulfonylureas or glinides, should be avoided in patients aged over 75; new-generation drugs are preferred.
G. In geriatric patients with impaired kidney function, dipeptidyl peptidase-4 inhibitors (DPP-4i) should be preferred over metformin, that remains the first line therapy otherwise.
H. Short-acting insulin analogs are preferred for insulin therapy. For basal insulin therapy in geriatric patients, second-generation analogs are recommended because of their favorable safety profile.

Hypoglycemia

A. Level 1 hypoglycemia (a measurable glucose concentration < 70 mg/dL - 3.9 mmol/l but ≥ 54 mg/dl - 3.0 mmol/l) in a conscious patient should be managed by administering glucose orally.
B. Level 2 (glucose concentration < 55 mg/dL independent of symptoms) or 3 (independent of measured glucose but requiring external assistance due to severe cognitive impairment) hypoglycemia requires intravenous administration of glucose and/or intramuscular glucagon.

Hyperglycemia and hyperosmolar coma

A. Attention should be paid to identify drug treatments, functional limitations, and comorbid diseases able to aggravate HHS in geriatric patients.
B. Conditions that lead to dehydration, like poor hydration of demented or disabled geriatric patients, and, then, predispose to both ketoacidosis and HHS, should be searched for and corrected.

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C. Rehydration and normalization of plasma osmolarity are key objective of the treatment.
D. Hospital-based care for HHS is recommended.

Diabetic ketoacidosis and ketoacidotic coma

A. The diagnosis of diabetic ketoacidosis should be made according to the following three parameters: glucose levels (generally greater than 250 mg/dl), acidosis (arterial pH less than 7.2), and ketone bodies present in the urine.
B. The diagnosis must be confirmed with arterial blood gas analysis in the presence of hyperglycemia.
C. In a non-hospital environment where arterial blood gas analysis is not available, diagnosis can be guided by the presence of Kussmaul breathing and breath acetone.
D. Conditions increasing the risk of diabetic ketoacidosis, like absolute or total insulin deficiency, or the use of Metformin or Sodium-Glucose Linked Transporter-2 inhibitors (SGLT-2i), should be searched for and amended.
E. Diabetic ketoacidosis should be treated with rehydration and insulin infusion (parenteral route) in a hospital setting.
F. Residual neurologic symptoms should be considered a key to a diagnosis of brain edema related to inadequate or late treatment of diabetic ketoacidosis.

2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is moderate to high. Recommendations are supported by published evidence and best practice (supported by expert opinion).

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Recent clinical trials on the new anti-hyperglycaemic drugs have enabled us to reconsider the treatment of glycemic syndromes in geriatric patients. Clinical results with cardiovascular outcomes (CVOTs) have opened new educational frontiers and fields of interest in geriatrics. Unfortunately, these studies do not show specific results in geriatric populations. Interpretations of these results make it possible to make indirect deductions for patients over 75. Uncertainty exists about safety and efficacy of nasal glucagon powder preparations.

APPENDIX

Diabetes complications in geriatric patients (e.g., falls or fainting caused by hypoglycemia)

The main acute complications of glucose homeostasis in geriatric patients are hypoglycaemia, severe hyperglycaemia with hyperosmolar plasma, also known as Hyperosmolar Hyperglycemic State (HHS), and diabetic ketoacidosis (DKA) leading to ketoacidosis coma. In geriatric patients, these conditions, which are common both in T1DM and T2DM, are significant events considered as medical emergencies, which can lead to death or permanent disability. These complications often occur during the management of geriatric DM patients, both at home and during hospitalization. HSS and DKA can co-occur, which adds to the clinical complexity, making them more difficult to identify, with a worse prognosis than when HHS or DKA occur alone [1]. DKA can also be caused by drugs, such as SGLT2 inhibitors, even when the patient's blood sugar is not particularly high. There are several pathophysiological mechanisms by which SGLT2 inhibitors could facilitate the development of DKA under low hyperglycaemia conditions, including: decrease in insulin secretion; increase of beta oxidation; possible increase in the secretion of glucagon directly or indirectly induced by these drugs [2,3]. The specifications (technical data sheet) of these drugs includes a warning about the potential risk of DKK.

These clinical conditions should also be suspected in patients without a known history of DM because DM is often underdiagnosed in the elderly due to comorbidities and polypharmacy. Although the management of these acute complications is relatively simple if initiated early, delays in diagnosis and treatment may result in permanent sequelae, including irreversible heart and brain damage. Indeed, these conditions are associated with a high mortality rate [4-6].

Hypoglycaemia, severe hyperglycaemia, and ketoacidosis often develop in geriatric patients with complex conditions such as age-related frailty. Therefore, during Comprehensive Geriatric Assessment the risk of developing complications linked to glycaemia should be evaluated; this clinical framework should be applied regardless of whether or not DM diagnosis or dysmetabolism is known [7]. Both insulin-sensitive tissue mass and pancreatic beta secretion decline with age [8-10], and typical age-related sarcopenia and parenchyma degeneration linked to physiological ageing affect the patients' insulin and glucose sensitivity. Altered tissue sensitivity to hormones that control glycemic homeostasis, associated with decreased insulin secretion and dysregulation of glucagon secretion, could be the initial etiopathogenetic cause of glycaemic imbalance [10-12].

The use of drugs that may influence glucose concentration, particularly glucocorticoids, could further aggravate these imbalances. Furthermore, given the nuanced symptomatology that usually characterizes hyper- and hypo-glycemia states (e.g., confusion, slurred speech, loss of consciousness, and falls), diagnosis is often missed or delayed. For example, falls or fainting in geriatric patients may be a clue to the presence of hypoglycemia, that must be taken into account in the differential diagnosis. Appropriate recognition and treatment could prevent further heart and brain damage (e.g., development of atrial fibrillation due to adrenergic stimulation secondary to hypoglycemia) [1].

Below, each of the three clinical conditions are discussed separately, highlighting the pathophysiological basis, main causes, therapeutic approaches, and specific characteristics of geriatric patients.

Hypoglycemia

Hypoglycemia is a commonly feared acute complication in DM patients, both for T1DM and T2DM, at any stage of life. However, in geriatric patients, due to conditions such as frailty, associated comorbidities, and polypharmacy, hypoglycemia may have particularly severe consequences. Therefore, understanding its causes and preventing it is an important objective in managing geriatric patients [7,13-15]. Common symptoms of hypoglycemia include tremor, tachycardia, sweating (adrenergic symptoms), disorientation, and loss of consciousness, as well as coma. Geriatric patients may not show these classic symptoms as diabetic autonomic neuropathy and drugs such as anti-psychotics and beta blockers can mask them. Moreover, many other age-related conditions may be associated with some of these symptoms [16,17]. It Is obviously easier to suspect hypoglycaemia in patients who already have a DM diagnosis and use insulin. Insulin therapy increases the risk of developing hypoglycemia, and both the patient and family members usually know the risks associated with this treatment. However, the potential danger of oral hypoglycemic agents, such as sulfonylureas or glinides, is often overlooked or underestimated. Due to their long plasma half-life and glucose-independent mechanisms of action, first- and second-generation sulfonylureas may increase the risk of hypoglycemia even more than insulin. Shorter-half-life drugs such as glinides, which are often more frequently prescribed in geriatric patients, also create potentially risky conditions for hypoglycemia due to their glucose-independent mechanisms. These drug classes, which can induce glucose-independent insulin release, can lead to severe and fatal hypoglycemic crises, due to their prolonged plasma half-life and possible interaction with other drugs. Current Italian and international guidelines advise against the use of this class of oral hypoglycemics in geriatric patients and recommend restricting use only to extreme conditions. In particular, glibenclamide should not be used in these patients [7,18]. Therefore, drug classes with a lower risk of hypoglycemia, some of which have recently been approved, should be used to achieve optimum glycemic targets even in geriatric patients with a low risk of hypoglycemia [7]. Obviously, the management of DM geriatric patients should be based on setting personalized glycemic targets, as reported in the recent treatment guidelines of the Italian Society of Diabetology (SID) and Italian Association of Medical Diabetologists (AMD), available at http://www.siditalia.it/clinica/linee-guida-societari.

New drugs for controlling glycaemia are available, which are safer in terms of the risks of hypoglycemia and are safer for geriatric patients, also from a cardiovascular perspective, particularly DPP-4 inhibitors. This class of drugs has been widely studied in geriatric patients, demonstrating greater safety and efficacy than traditional insulinotropic therapies [19]. Insulin analogs that have a very short-term action are available as well as new-generation basal insulins with more stable pharmacokinetic and pharmacodynamic profiles than first-generation insulins. However, there is a lack evidence from clinical trials on these new insulins specifically in geriatric patients [20-23]. Other treatment options for managing hyperglycaemia in DM patients include new classes of drugs that have an effect on blood glucose and positive pleiotropic effects on the heart, kidney, and brain. These new classes of drugs have good safety and tolerance profiles even in geriatric patients, although there are no clinical trials specifically designed for persons aged over 75 years. These drugs include GLP-1 and SGLT2-inhibitors. In particular, SGLT2-inhibitors have shown particular benefits for the heart and kidney, although in specific cases they have a potential risk of inducing ketoacidosis, especially in patients using insulin therapy. As a result of reports in the literature, the technical sheets for drugs on the market specify that treated patients can potentially develop DKA. This condition could also lead to further problems because it can also occur when glycaemia is not particularly high (euglycemic DKA) [24]. However, the use of these drugs in DM patients in recent years provide some reassurance about the risks, but there is still a valid need to be vigilant in patients using them.

Using drugs that are less likely to cause hypoglycemia can also have positive effects in terms of reducing the risk of hospitalization and long-term complications. Repeated episodes of hypoglycemia, even moderate cases, increase the risk of falls in geriatric patients, as well as cardiovascular events with permanent sequelae or coma [25]. It has also been reported that hypoglycemia

could have a pathophysiological basis for the development of dementia and chronic neurodegenerative diseases [26]. However, although this is still under debate, there may be a vicious circle that includes a risk of brain damage and an additional risk of uncontrolled glycaemia and, therefore, of developing hypoglycemia [27-29]. Recognizing the risk of hypoglycemia in individual patients, preventing its causes, recognizing symptoms, and rapidly managing hypoglycemic events clearly has a positive impact on the management of geriatric patients [7,18]. Hypoglycemic events can be managed with oral or intravenous administration of glucose, depending on the level of glycaemia detected. In general, this strategy should be taken when levels of glycaemia are less than 70 mg/dl but more than 54 mg/dl (Level 1), as it is the easiest way to restore glycaemia values in both younger and older individuals. However, treatment depends on the clinical presentation, whether the patient is unconscious, where it develops, and whether other people are present to help manage the problem. Therefore, early identification can also help to identify the best treatment and improve the final prognosis for this condition. A patient who has lost consciousness (defined as Level 3 according to guidelines) is more complex and needs help from a third-party to clinically improve [7,18]. When hypoglycema causes loss of consciousness, in addition to intravenous glucose patients should be treated with glucagone [7,18]. Some glucagon preparations can restore glycaemic levels, but they are not always available or they can be difficult to use because of their complex preparation methods. There are two glucagon products consisting of a dry powder and a liquid solvent in a separate syringe, which can be difficult to reconstitute, even for people who have been trained to use it. Recently, a ready-to-use nasal formulation that does not need preparation (Nasal Glucagon) [30] has been released in Italy. Other ready-to-use preparations are in the advanced stages of testing and have been approved for marketing in many countries around the world.

Hyperglycaemia and hyperosmolar coma

Hyperglycaemia is a metabolic condition characteristic of DM, which can be associated with the patient's health condition, comorbidities, and drug therapy. It can be an acute event that can lead to coma and an increased risk of death. In particular, hyperosmolar hyperglycemic state (HHS), is a serious acute event, especially for geriatric patients, and is associated with a high mortality risk [4-6]. Common mechanisms underlying this clinical syndrome include dehydration, deficiency or lack of insulin, and dysregulation of insulin counter-regulatory hormones, especially glucagon, cortisol, and catecholamines [1,31-37].

Although HHS is more typical in geriatric patients, and the development of DKA is more frequent in younger patients and those with T1DM, both can occur at the same time in geriatric patients and can be complicated by the type of therapy, comorbidities, and the patient's general condition [34,38,39]. HHS and DKA (which will be covered in more detail later) are conditions that cause a high mortality risk in geriatric patient. Geriatric patients with impaired glicemic control but without an established diagnosis of diabetes may be paradoxically at higher risk for hyperglycemic crises due to dehydration; these patients need to be adequately hydrated [31,40].

The management of geriatric patients can be negatively affected by poor treatment or lack of treatment, particularly in situations where they are institutionalized or supported by untrained family members or informal caregivers. Moreover, adipsia can worsen the state of these patients; a thorough anamnesis is needed to identify these conditions. Kidney failure and dehydration can lead to increased plasma osmolarity in geriatric patients. A diagnosis of HHS typically occurs in patients with T2DM, both in persons with undetected DM and those with a recognized diagnosis. Often, insulin deficiency is not the initial reason for the condition. Compared to DKA, where insulin deficiency is the basis of the clinical syndrome, onset is more gradual and the diagnostic criteria are different; for HHS patients, glycaemia often reaches very high values (greater than 400 mg/dl), with increased plasma osmolarity values (greater than 350 mOsm/kg). Chetonuria is generally absent and blood pH is never below 7.3. This differentiates HHS from DKA, where these parameters are different. However, the root causes of DKA and HHS may be the same: dehydration, infection, sepsis, vomiting, or fasting.

Although treatment should be individualized, once HHS has been diagnosed therapy includes rehydration and insulin treatment, and it is more easily controlled in a hospital environment [37]. The most appropriate treatment should be chosen according to glycaemic levels, plasma osmolarity, and the patient's general health status and clinical presentation, and rehydration, electrolytes, and insulin should be considered. Early identification can also help to identify the best treatment and improve the final prognosis for this condition.

DKA and ketoacidosis coma

The following three signs are needed to make a diagnosis of DKA: high glucose levels (generally greater than 250 mg/dl), acidosis (arterial pH below 7.2) and ketones in urine. Although DKA diagnosis is easy to make in hospital settings, it is often complicated in the home environment. In home settings it is only possible suspect the diagnosis of DKA based on the presence of

ketones in urine, when available, because arterial blood gas tests cannot be conducted. However, diagnosis can also be supported by looking at the clinical presentation; individuals with DKA often have abdominal pain, Kussmaul breathing, and acetone breath, in addition to the usual symptoms of hyperglycemia such as polyuria, polydipsia, polyphagia, slurred speech, and impaired cognition, however, these signs are also common in other clinical conditions that affect geriatric patients, including prolonged fasting, hyperemesis, or alcohol consumption [24]. In these patients, as for HHS, euglycemia needs to be restored, improving insulin levels, as this is often the basis for developing DKA. In addition, the use of certain oral hypoglycemic drug classes, including metformin and SGLT2 inhibitors, can lead to a state of ketosis even when glycaemia is normal or slightly increased (euDKA). In such cases, glycaemic levels usually do not exceed 200 mg/dl but low levels of arterial pH are present; there are also ketone bodies in the urine if the patient is taking SGLT2 inhibitors [24]. The use of SGLT2 inhibitors in insulin-treated patients can lead to a reduction in insulin doses, specifically because of the rapid improvement in glycemic compensation, leading to relative insulin deficiency. Relative insulin deficiency could be the basis of many recently reported DKA episodes, confirming theories about the pathophysiological bases underlying euglycemic DKA. Investigating the use of these drugs could help clinicians with diagnosis and treatment. DKA is extremely dangerous for geriatric patients if it is not treated rapidly, and leads to loss of consciousness, coma, and death [41]. It should be noted that DKA treatments, i.e., parenterally administered fluids and insulin, can cause brain edema. Although rare, this depends on how rapidly hydroelectrolytic and metabolic balance is restored. Brain edema is a complication that can cause death, estimated at approximately 24% [24,42] and this risk should be taken into account when identifying and treating DKA in geriatric patients. Geriatric DM patients who are undergoing insulin treatment with or without metformin and/or SGLT2 inhibitors and their family should be informed of the risks so that they can rapidly recognize and monitor them.

Ethical consideration
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Conflict of interest
The Authors declare no conflict of interest.

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This statement is:	**Quality of the evidence** (in the case of recommendation):
☒ **Recommendation** (supported by published evidence) ☒ **Best practice** (supported by expert opinion)	☐ Low ☒ **Moderate** ☐ High