Chapter

Prevention of Hyperglycemia

Lucy A. Ochola and Eric M. Guantai

Abstract

Hyperglycemia is the elevation of blood glucose concentrations above the normal range. Prolonged uncontrolled hyperglycemia is associated with serious life-threatening complications. Hyperglycemia arises from an imbalance between glucose production and glucose uptake and utilization by peripheral tissues. Disorders that compromise pancreatic function or affect the glucose counter-regulatory hormones cause hyperglycemia. Acute or serious illness or injury may also bring about hyperglycemia, as can many classes of drugs. Metformin lowers blood glucose levels by inhibiting the production of glucose by the liver whilst enhancing uptake of circulating glucose and its utilization in peripheral tissues such as muscle and adipose tissue. Metformin suppresses hepatic gluconeogenesis by inhibiting mitochondrial respiration and causing a reduction of cellular ATP levels. Metformin may also modulate the gut-brain-liver axis, resulting in suppression of hepatic glucose production. Metformin also opposes the hyperglycemic action of glucagon and may ameliorate pancreatic cell dysfunction associated with hyperglycemia. Metformin is therefore recommended for use in the prevention of hyperglycemia, including drug-induced hyperglycemia, in at risk patients. The benefits of metformin in the prevention of hyperglycemia are unmatched despite its contraindications.

Keywords: hyperglycemia, hyperinsulinemia, insulin, metformin, glucose

1. Introduction

Chronic hyperglycemia can lead to complications involving damage to the kidneys, retina, nervous system and cardiovascular system. In this chapter, we discuss the causes of hyperglycemia, including drug-induced hyperglycemia, highlighting the importance and approaches to prevention and management of hyperglycemia. We focus on the role and rationale for the use of metformin for the prevention of hyperglycemia, presenting the evidence that supports its use for this indication.

2. Hyperglycemia

Hyperglycemia, which literally means 'high blood glucose' levels, refers to the elevation of blood glucose concentrations above the normal range. Specifically, it refers to fasting blood glucose levels greater than 7.0 mmol/L (126 mg/dl) or 2-hour postprandial blood glucose levels greater than 11.0 mmol/L (200 mg/dl) [1].

2.1 Symptoms and complications

Mild, transient hyperglycemia is largely asymptomatic. However, prolonged uncontrolled hyperglycemia is associated with various symptoms including the

classic hyperglycemic triad of polyuria, polydipsia, and polyphagia, as well as blurred vision, dehydration, weight changes (gain or loss), generalized fatigue, abdominal discomfort, nausea, vomiting and muscle cramps [1, 2]. Complications arise when the hyperglycemia is severe and/or persists over an extended period. Frequent infections, erectile dysfunction and poor wound healing are associated with prolonged hyperglycemia. Chronic hyperglycemia can also lead to many serious life-threatening complications involving damage to the kidneys (nephropathy), retina (retinopathy), nervous system (peripheral neuropathy) and cardiovascular system (myocardial infarction, stroke) [1–5].

2.2 Causes of hyperglycemia

Blood glucose levels reflect the dynamic balance between, on the one hand, dietary glucose absorption and hepatic glucose production and, on the other hand, glucose uptake and utilization by peripheral tissues. Except for dietary glucose absorption, these complex and interrelated processes are under the control of the hormone insulin and, to a lesser extent, other counter-regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone [1, 6]. Hyperglycemia arises from an imbalance in these processes that determine blood glucose levels.

The greatest quantitative determinant for hyperglycemia is dysfunction in pancreatic islet cell activity which affects insulin release from the pancreas in response to. The pathophysiology of hyperglycemia also entails a resulting degree of insulin resistance and impairment in homeostatic glucose regulation. Insulin resistance results in decreased uptake of glucose by insulin-sensitive tissues as well as a consequential increase in endogenous glucose production. This all leads to hyperglycemia [7]. The elevation of blood glucose levels during the fasting state is directly proportional to the increase in hepatic glucose production while that of the postprandial state is connected to insufficient suppression of glucose output plus a defect in the stimulation of insulin hormone on recipient tissues like skeletal muscle [8].

The progression of this imbalance in blood glucose homeostasis over time leads to the development of diabetes, a chronic disease affecting glucose metabolism that occurs due to either insufficient production of insulin by the pancreas, or inadequate response by tissues to insulin [9]. The development of diabetes can be delayed or prevented by targeting the early prevention and/or reversal of hyperglycemia, as well as by inhibiting the development of hyperinsulinemia-induced insulin resistance [10]. This would also delay progression of prediabetic states to diabetes [11].

In addition to diabetes, there are a myriad of other causes of hyperglycemia, i.e., non-diabetic hyperglycemia. Disorders that compromise pancreatic function (pancreatic cancer, cystic fibrosis, chronic pancreatitis, etc.) or affect the glucose counter-regulatory hormones (pheochromocytoma, acromegaly, Cushing syndrome) cause hyperglycemia. Transient hyperglycemia may arise consequent to abnormally high carbohydrates in the diet, dextrose infusion and total parental nutrition. Acute or serious illness or injury may also bring about transient hyperglycemia referred to as stress hyperglycemia or hospital-related hyperglycemia [1, 12].

Medicines may also induce hyperglycemia [1, 6, 13].

2.3 Drug-induced hyperglycemia

Drug-induced hyperglycemia refers to the clinically relevant elevation of blood glucose levels caused by drugs [13]. Whereas drug-induced hyperglycemia is often mild and asymptomatic, severe hyperglycemia may occur particularly in predisposed patients, such as those with pre-existing pancreatic dysfunction or insulin resistance. Drug-induced hyperglycemia can occur in adults and children alike,

and certain patient factors are known to increase the risk of drug-induced hyperglycemia, such as obesity, sedentary lifestyle, stress, illness, history of gestational diabetes, or a family history of diabetes [6, 14].

Many classes of drugs have been implicated in causing hyperglycemia via various mechanisms. Some drugs cause hyperglycemia by reducing insulin production/secretion (glucocorticoids, β-receptor antagonists, thiazide diuretics, calcium-channel blockers, phenytoin, pentamidine, calcineurin inhibitors, protease inhibitors), including by direct damage to pancreatic cells (glucocorticoids, pentamidine, statins). Glucocorticoids, β-receptor antagonists and thiazide diuretics also promote hepatic glucose production and reduce insulin sensitivity. Other classes of drugs that reduce peripheral tissue sensitivity to insulin include atypical antipsychotics, antidepressants, oral contraceptives, statins, nucleoside reverse transcriptase inhibitors and protease inhibitors [1, 6, 14–16]. Hyperglycemia is one of the common adverse effects of the anticancer agent L-asparaginase, which inhibits insulin synthesis by depleting available asparagine in pancreatic cells in addition to impairing insulin receptor activity and promoting peripheral tissue resistance to insulin [14]. Monoclonal antibodies such as nivolumab and pembrolizumab may cause severe hyperglycemia by triggering the autoimmune-mediated destruction of pancreatic cells [17, 18]. β_2-receptor agonists cause hyperglycemia by promoting hepatic and

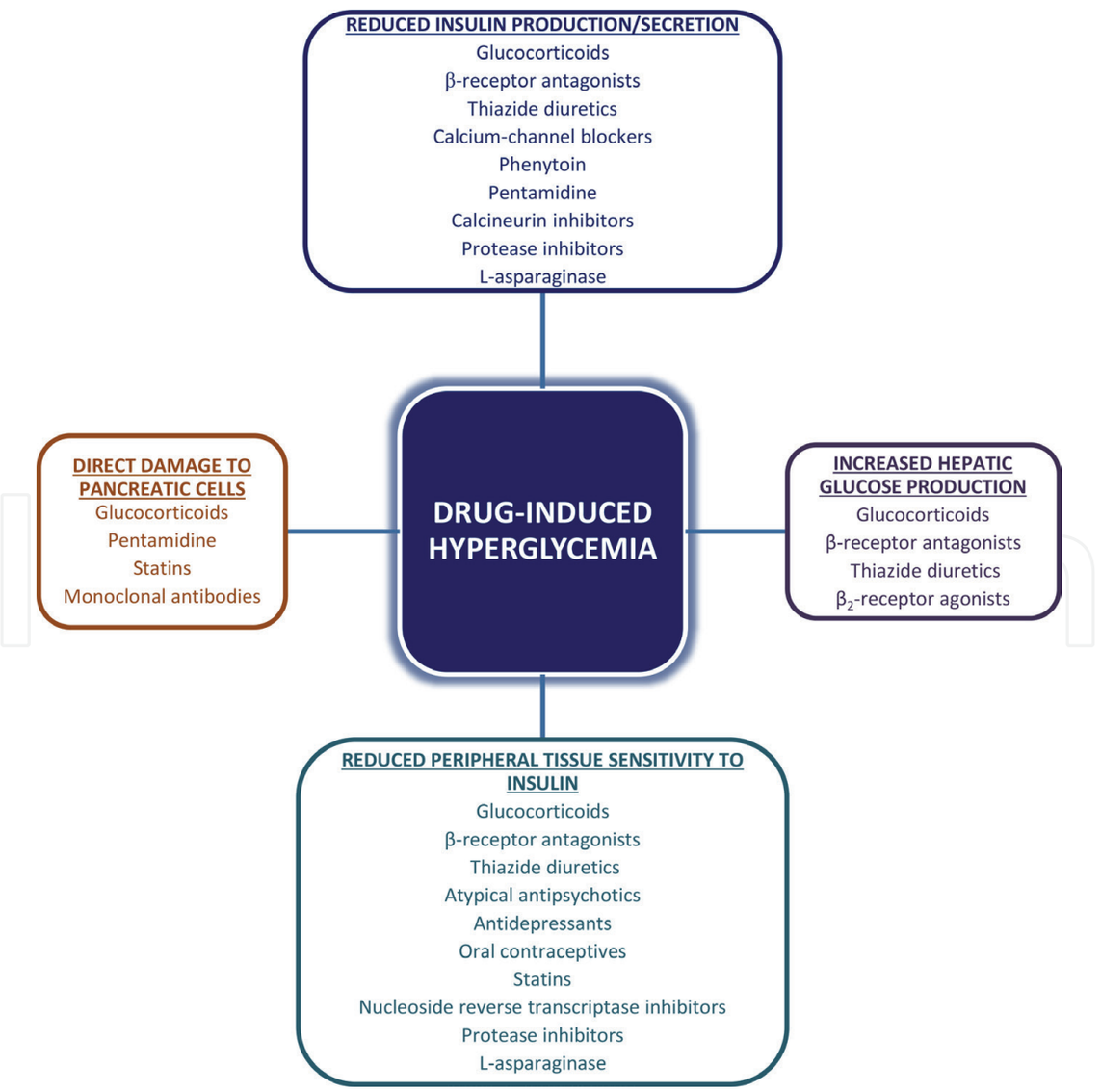

Figure 1.
Mechanisms of drug-induced hyperglycemia and implicated classes of drugs.

muscle glucose production [19]. The various mechanisms of drug-induced hyperglycemia and the classes of drugs implicated are shown in **Figure 1**.

The overall occurrence of drug-induced hyperglycemia is not known and would obviously vary between individual drugs. There is a lack of data on the burden of drug-induced hyperglycemia for specific drugs, and a few studies have attempted to address this gap. For example, the incidence of corticosteroid-related hyperglycemia in patients treated with high dose corticosteroids has been estimated to be in excess 50% [20, 21]. Comparably high prevalence has been reported for clozapine [22]. These and other similar findings strongly suggest that the risk of drug-induced hyperglycemia (alongside the risk of new-onset diabetes) is real.

The onset of drug-induced hyperglycemia varies on the medication administered. At the time of or shortly after initiating corticosteroids, blood glucose levels may be altered, whereas patients on hydrochlorothiazide may not experience altered levels for weeks or longer, depending on the dose given. In regard to second generation antipsychotics (SGAs), a consensus statement developed by the American Diabetes Association (ADA) in conjunction with other medical organizations recommends monitoring fasting blood glucose for 12 weeks after initiation of therapy and annually thereafter in those without diabetes. However, cases involving hyperglycemic crises have been reported within weeks of starting SGAs [23].

3. Prevention and management of hyperglycemia

The common medical occurrence of hyperglycemic states has yet to be given the due attention it deserves, considering the numerous consequences it bears to patients and the healthcare fraternity. The existing reality of numerous patients suffering from hyperglycemia of varied cause provides an overwhelming patient load, unmatched by the number of specialized providers. However, the management of hyperglycemia has continually posed a great challenge mainly from a lack of standardized protocols [24]. Currently, lack of knowledge and consensus on strategies of management play a significant role in its mismanagement.

Insulin resistance and the resulting compensatory hyperinsulinemia is considered to preclude the development of type 2 diabetes. Hyperglycemia prophylaxis is thus highly attractive based on the numerous socio-economic benefits it confers to patients and the healthcare system. Several studies have demonstrated the advantages gained from preventing elevations of blood glucose levels across a divergent patient portfolio. Research has broadly focused on management of hyperglycemia regardless of the cause, which underlies the common pathways involved in the development of hyperglycemia.

3.1 The role of insulin

The primary strategy employed in hyperglycemia management is insulin [25]. Consensus arrived at by ADA and European Association for the Study of Diabetes (EASD) outline the management of hyperglycemia in type 2 diabetes patients. These guidelines have also been adopted in the prevention of hyperglycemia from other causes, including drug-induced hyperglycemia. The guidelines recommend the use of insulin in all hospitalized patients, with discontinuation of oral hypoglycemic medication [26, 27]. Stoppage of the drugs is on the basis that majority of hospitalized patients present with concurrent conditions and/or physiological dysfunctions that tend to contraindicate continued use of these medications if already prescribed. The pharmacokinetics of oral medication, which tend to have a slow onset of action, disallows for rapid dose adjustment to changing patient needs [28].

Therefore, it is recommended that critically ill patients be treated with a continuous insulin infusion while non-critically ill patients are initiated on subcutaneous (SC) insulin. An individualized dose adjustment for insulin is advised across major studies [26, 29]. Resumption of oral diabetic agents (ODA) when transitioning from inpatient to outpatient setting, with careful consideration given to previous insulin dosing, is advised upon successful treatment. A study involving patients without diabetes recommended the administration of intravenous (IV) insulin infusion in patients with serum blood glucose level values of greater than 10 mmol/L, with a target of achieving serum blood glucose levels of 7.8–10 mmol/L in non-critical settings and less than 7.8 mmol/L in an outpatient setting [30].

Despite numerous recommendations, challenges faced by providers during insulin administration cannot be overlooked. The biggest impediment to insulin use in management of drug-induced hyperglycemia in the affected population is the unavoidable side effect of hypoglycemia [31]. Unfortunately, insulin treatment is the most common risk factor for inpatient hypoglycemia. The incidence of hypoglycemia is approximately 30% in elderly patients, in spite of using low dose insulin and oral diabetic agents [28]. This is associated with increased mortality rate and prolonged hospital stays. Hence, constant monitoring of blood glucose levels is necessary.

Dose adjustments using patients' weight is perceived to be safe and effective as long as close monitoring is done. However, this is not always feasible, let alone practical with many patients. So too is the recommendation of individualizing glycemic targets for patients based on clinical status, risk of hypoglycemia and patient comorbidities, no matter the benefit it confers. This is because the number of patients with drug-induced hyperglycemia cannot be matched to the number of specialized health care workers required to meet this need.

Herein lies the difficulty as many patients are unable to achieve the close monitoring desired, let alone manage the expected side effects in a home-based set up. Even in hospitalized patients, lack of protocols for dose adjustment poses a hindrance in adequate control of elevated blood glucose levels. Hypoglycemia presents a consequential effect that should be carefully considered in hyperglycemia management. Any chosen medication, in addition to lifestyle interventions, should ideally be one that is safe, effective, economical and with minimal side effects.

3.2 The role of oral antidiabetic medications

Non-insulin medications provide a practical alternative to achieving glycemic control. These agents may also confer a non-glycemic benefit whilst regulating the fluctuations in blood glucose levels. Alternatives among non-insulin medication include metformin, sulphonylureas, glinides, thiazolidinediones, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium–glucose cotransporter2 (SGLT2) inhibitors.

However, the side effects of each of these agents must also be considered. For example, SGLT2 inhibitors reduce blood glucose levels by preventing proximal tubular reabsorption in the kidney. This has been shown to effectively reduce glycated hemoglobin A1c (HbA1c) levels by 0.6–1.0%. They are also associated with a low risk of hypoglycemia. However, the dehydration side effects make these agents contraindicated in renal dysfunction. They also bear an increased risk of urinary and genital tract infections and are related with the development of diabetic ketoacidosis among diabetic patients [32]. Such a profile tends to limit the use of these agents. Metformin use is contraindicated in the presence of any possible indication for iodinated contrast media and in renal insufficiency while thiazolidinediones are associated with fluid retention. On the other hand, sulfonylureas and glinides

result in hypoglycemia in most patients while GLP-1 receptor antagonists can cause nausea and hence need to be withheld in critical patients. In spite of the many side effects of oral diabetic agents and the recommendation of using insulin as first line, recent studies have leaned towards the adoption of the oral diabetic agents. The drug most endorsed based on clinical evidence has been metformin [33].

4. Metformin for the prevention of hyperglycemia

4.1 Introduction and rationale

The pathophysiology of hyperglycemia entails a degree of insulin resistance and results in decreased uptake of glucose by insulin-sensitive tissues as well as a consequential increase in endogenous glucose production [7]. Dysfunction in the activity of pancreatic islet cells affects insulin release in response to rising blood glucose levels. Targeting the prevention and/or reversal of dysglycemia and insulin resistance is the principal behind preventing the development of hyperglycemia [11]. Any agent used in prevention of hyperglycemia must therefore target these pathways, thereby partially or completely eliminating its development.

Metformin can rightfully be considered for hyperglycemia prevention and treatment in cases of insulin resistance. Metformin is a first-line agent in treatment of type 2 diabetes mellitus. Recent studies have shown it confers a greater benefit to patients than the other oral diabetic agents, which has led to its recommendation for use in the prevention of hyperglycemia and prediabetes in at risk patients [34–36].

4.2 Mechanisms of action/pharmacodynamics

Metformin prevents hyperglycemia by hastening the clearance of glucose [37, 38]. It causes a reduction in hyperglycemia and hyperinsulinemia [39]. This facilitates a consequent decline in high insulin and high blood glucose levels, with no effect on insulin secretion. The primary mechanism involved in lowering blood glucose levels is through improving hepatic and peripheral tissue sensitivity to insulin [40]. It inhibits the production of glucose by the liver whilst enhancing uptake of circulating glucose and its utilization in peripheral tissues such as muscle and adipose tissue.

Hepatic gluconeogenesis is an energy-demanding process in which synthesis of one molecule of glucose from lactate or pyruvate requires four molecules of ATP and two molecules of GTP. Metformin suppresses hepatic gluconeogenesis by causing a reduction of cellular ATP levels [41]. Molecularly, metformin appears to inhibit mitochondrial respiration. The resulting shift in cellular energy balance increases the activity of AMP-activated protein kinase (AMPK), which promotes the action of insulin and reduces hepatic gluconeogenesis [42]. AMPK acts as a cell energy sensor: it plays a role in energy balance at the cellular and body level by adapting to changes in the concentration of AMP/ADP relative to ATP [43]. Upon activation by a decrease in cellular energy levels, AMPK initiates a change from anabolic to catabolic pathways that consume ATP. This stimulates the uptake and use of glucose and oxidation of fatty acids, in addition to the suppression of hepatic glucose production. Metformin's' inhibition of the mitochondrial complex is the basis of its effect as observed through the change in the ratios of AMP/ATP or ADP/ATP after its administration [44]. Multiple studies have demostrated that one of the mechanisms of action of metformin is the disruption of mitochondrial complex I [45, 46].

Metformin may also modulate the gut-brain-liver axis through the activation of a duodenal AMPK-dependent pathway, as has been demonstrated in rats. This effect

involves activation of protein kinase A (Pka) by GLP-1 in duodenal enterocytes, and results in suppression of hepatic glucose production [47]. It has been shown that glucocorticoid therapy leads to changes in the activation of AMPK in Cushing's syndrome patients and in vitro in human adipocytes, effects that were reversed with metformin in human adipocytes. These indicate the likelihood of converse effects of steroids and metformin in the AMPK signaling pathway, as well as the overriding of steroid effects by metformin [44, 48]. Supporting studies demonstrate that steroid-related increase in glucose levels can be prevented with an AMPK activator [49].

Another postulated mechanism of action for metformin is by causing an increase in circulating cyclic adenosine monophosphate (cAMP) which in turn opposes the hyperglycemic action of glucagon [42, 50]. Metformin has also been postulated to increase the concentration of Glucagon-like peptide-1 (GLP-1) by enhancing site production as well as subsequently decreasing its degradation in circulation and specific tissues via inactivation of the enzyme dipeptide peptidase-4 (DPP-4). Additionally, metformin may induce up regulation of GLP-1receptors on beta cell surfaces of the pancreas. This can aid in ameliorating the beta cell dysfunction associated with hyperglycemia via the enhancement of the role of GLP-1 on glucose dependent release of insulin [11].

4.3 Metformin prevents hyperglycemia and hyperinsulinemia

Metformin can rightfully be considered for hyperglycemia prevention and treatment in cases of insulin resistance. Metformin has been identified as a first line agent in treatment of type 2 diabetes mellitus. Recent studies have shown that it confers a greater benefit to patients than the other oral diabetic agents, which has led to its recommendation for use in the prevention of prediabetes in at risk patients [34, 35, 51]. Presently though, only a few nations have formally adopted this proposal such as Poland, Philippines and Turkey but many may adopt it in the near future based on the emerging evidence [11]. Metformin overrides most of the factors that contribute to poor glycemic management like inaccessibility to medicine and fear of developing hypoglycemia. This improves patient perception on its use regardless of the minimal side effects. In addition, it has been demonstrated to confer long term benefit to those who use it prophylactically. A study that followed up patients from a diabetes prevention program after 15 years found that the metformin treatment arm had a 17% lower incidence for developing type 2 diabetes than the placebo arm. This was determined using the HbA1c parameter, in which 36% of the patients had a risk reduction for diabetes development [34].

In a prospective observational study in persons with normal glucose tolerance and hyperinsulinemia, a dose of 2.55 ± 0.2 g/day of metformin restored physiological insulin secretion by decreasing fasting and post-glucose load hyperinsulinemia in the oral glucose tolerance test (OGTT). Over the observation period, the effect of metformin on the reduction of hyperinsulinemia increased over time, peaking after 1 year of treatment. The ability to lower fasting blood glucose levels also improved with time. Fasting blood glucose levels reached normoglycemic range at 3 months and remained so until the end of the 1 year observation period, with no development of hypoglycemia [39]. A substantial decrease in hyperinsulinemia from high blood glucose levels has also been reported in metformin-treated patients based on an increase in the uptake of glucose [52]. The enhancement of insulin action reduces the load on the beta cells in insulin secretion thus can aid in ameliorating the beta cell dysfunction to an extent; this confers an advantage to patients predisposed to developing hyperglycemia.

In addition, a randomized controlled study showed that there was no significant difference in blood glucose levels between critically ill patients receiving 1000 mg

of metformin daily versus a similar spectrum of patients receiving 50 International Units (IU) of regular insulin. Furthermore, metformin-treated patients had blood glucose levels subside to near-normal range [40]. The targeted desired blood glucose levels were achieved with metformin after three days while insulin failed to do the same.

4.4 Metformin for drug-induced hyperglycemia

In acute lymphoblastic leukemia patients with drug-induce hyperglycemia, metformin monotherapy controlled blood glucose in 12 out of 17 patients, without the need for insulin using a median dose of 1000 mg/day for a median of 6 days. Blood glucose levels never exceeded 11.1 mmol/L in 8 of the 12 patients. The one patient who developed hyperglycemia during relapse re-induction for leukemia treatment was effectively controlled using metformin alone [53]. Three of the patients given insulin therapy due to high blood glucose levels were eventually weaned off insulin to metformin alone. Additionally, in a controlled trial consisting of non-diabetic patients on glucocorticoids, metformin prevented an increase of 2-hour glucose AUC with, signifying glucose tolerance preservation. No changes in baseline and after 4 weeks metformin treatment was seen with the 2-hour glucose AUC whereas this parameter increased in the placebo group [54].

Similarly, the effect of metformin on prednisone-induced hyperglycemia (PIH) was observed on fasting and 2-hour post prandial glucose levels in hematological cancer patients. The fasting blood glucose readings indicated a proportion of prednisone-induced hyperglycemia of 72.7% and 14.3% in the control and treatment groups respectively. The proportion was slightly lower while using the 2-hour post prandial glucose, in which 54.5% of participants in the control group developed prednisone-induced hyperglycemia while none developed prednisone-induced hyperglycemia in the treatment group. Patients in the control group had 16 (95% CI 1.3–194.6) times the odds of developing prednisone-induced hyperglycemia compared to patients in the treatment group. Double daily dosing (1700 mg twice daily) was more effective in preventing prednisone-induced hyperglycemia [21]. This is supported by other studies that show that that a daily dose of metformin 1500 mg contributes to 80–85% glucose lowering effects [55].

4.5 Metformin for hyperglycemia: risks and benefits

The limitations attached to the full exploitation of metformin use include its relative contraindications in many hospitalized patients who present with comorbidities like renal insufficiency or unstable hemodynamic status. Metformin is contraindicated if serum creatinine is ≥133 mmol/L in men or ≥ 124 mmol/L in women. Emerging evidence shows that the established cut-off points for renal safety may be overly restrictive [56]. It has been argued that there is a need to relax these cut-offs and policies to allow use of this drug to patients with stable chronic kidney disease characterized by mild–moderate renal insufficiency [57–59].

The associated risk of lactic acidosis tends to deter the use of metformin in majority of the comorbid patients on drugs that predispose to the development of hyperglycemia. However, the studies that made such recommendations used a small percentage of the patient population, thus limiting the extrapolation of these recommendations to the greater public [60]. Fortunately, the incidence of metformin-induced lactic acidosis is rare and can be significantly reduced in at-risk patients by observing the necessary precautions [27, 56]. Other factors may also play a greater role in in being predictors of acidosis, such as dehydration, severe heart and renal failure. Thus, its benefits for use outweigh the potential risk of lactic acidosis.

Supporting evidence on avoidance of metformin use in certain cases is poor and inconsistent such as in patients undergoing radio-contrast imaging which theoretically predisposes patients to media-induced nephropathy, increasing the risk of lactic acidosis [56].

The benefits of metformin in the prevention of hyperglycemia are unmatched despite its list of contraindications. This has facilitated its expanded use based on its well-founded glycemic effects as well as numerous benefits conferred such as the beneficial effect on reduction of development of cardiovascular risk factors [61]. It confers good glycemic management that yields a substantial and enduring decrease in the onset and progression of micro vascular complications [60].

Moreover, large based clinical trials and systematic reviews have shown its beneficial effect of enhancing weight loss, even the weight loss associated with medicaments like antipsychotic agents [62, 63].

5. Conclusions

In summary, the suppression of glucose production by metformin's direct effect plus the enhancement of hepatic insulin signaling will curb the development of drug-induced hyperglycemia. Metformin has been shown to reduce the incidence of hyperglycemia-related complications such as diabetes and risk factors for cardiovascular disease in patients with impaired glucose tolerance and fasting blood sugar [11, 64, 65]. This has led to its endorsement of use in patients with high risk of developing the aforementioned conditions [36].

Author details

Lucy A. Ochola[1*] and Eric M. Guantai[2]

1 Machakos Level 5 Hospital, Machakos, Kenya

2 School of Pharmacy, University of Nairobi, Nairobi, Kenya

*Address all correspondence to: lucyochola@gmail.com

References

[1] Mouri Mi, Badireddy M. Hyperglycemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jun 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK430900/

[2] Utiger RD. Hyperglycemia [Internet]. Encyclopedia Britannica. [cited 2021 Jun 18]. Available from: https://www.britannica.com/science/hyperglycemia

[3] Chao JH, Hirsch IB. Initial Management of Severe Hyperglycemia in Type 2 Diabetes. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. South Dartmouth (MA); 2000.

[4] Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. 2020 Jul;16(7):377-90.

[5] Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016 Jun;37(3):278-316.

[6] Fathallah N, Slim R, Larif S, Hmouda H, Ben Salem C. Drug-Induced Hyperglycaemia and Diabetes. Drug Saf [Internet]. 2015;38(12):1153-68. Available from: https://doi.org/10.1007/s40264-015-0339-z

[7] Thorell A, Rooyackers O, Myrenfors P, Soop M, Nygren J, Ljungqvist OH. Intensive insulin treatment in critically ill trauma patients normalizes glucose by reducing endogenous glucose production. J Clin Endocrinol Metab. 2004 Nov;89(11):5382-6.

[8] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach. Diabetes Care. 2012;35(6):1364-79.

[9] Diabetes [Internet]. [cited 2021 Jun 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes

[10] Kamenova P. Therapeutic potential of metformin in normal glucose tolerant persons with metabolic syndrome. Biotechnol Biotechnol Equip [Internet]. 2020;34(1):30-7. Available from: https://doi.org/10.1080/13102818.2019.1711184

[11] Hostalek U, Gwilt M, Hildemann S. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs. 2015;75(10):1071-94.

[12] Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! Crit Care. 2013 Mar;17(2):305.

[13] Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA. 2001 Oct;286(16):1945-8.

[14] Tosur M, Viau-Colindres J, Astudillo M, Redondo MJ, Lyons SK. Medication-induced hyperglycemia: pediatric perspective. BMJ open diabetes Res care. 2020 Jan;8(1).

[15] Frontoni S, Picconi F. Impact of Drugs on Diabetes Risk and Glycemic Control. In 2019.

[16] Jain V, Patel RK, Kapadia Z, Galiveeti S, Banerji M, Hope L. Drugs and hyperglycemia: A practical guide. Maturitas. 2017 Oct;104:80-3.

[17] Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol. 2017 Apr;13(4):195-207.

[18] de Filette JMK, Pen JJ, Decoster L, Vissers T, Bravenboer B, Van der

Auwera BJ, et al. Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. Eur J Endocrinol. 2019 Sep;181(3):363-74.

[19] Smith AP, Banks J, Buchanan K, Cheong B, Gunawardena KA. Mechanisms of abnormal glucose metabolism during the treatment of acute severe asthma. Q J Med. 1992 Jan;82(297):71-80.

[20] Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocr Pract [Internet]. 2006 Jul 1;12(4):358-62. Available from: https://doi.org/10.4158/EP.12.4.358

[21] Ochola LA, Nyamu DG, Guantai EM, Weru IW. Metformin's effectiveness in preventing prednisone-induced hyperglycemia in hematological cancers. J Oncol Pharm Pract [Internet]. 2019 Sep 7;26(4):823-34. Available from: https://doi.org/10.1177/1078155219873048

[22] Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry. 2000 Jun;157(6):975-81.

[23] Touger J. Introductory physics : building understanding. Diabetes Care. 2006;27(2):904.

[24] Abernathy E, Glaunsinger B. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company' s public news and information. 2020;(January).

[25] Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2004 Oct;164(18):2005-11.

[26] Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(1):16-38.

[27] Kodner C, Anderson L, Pohlgeers K. Glucose Management in Hospitalized Patients. Am Fam Physician. 2017;96(10):648-54.

[28] Umpierrez GE, Pasquel FJ. Management of inpatient hyperglycemia and diabetes in older adults. Diabetes Care. 2017;40(4):509-17.

[29] Magaji V, Johnston JM. Inpatient management of hyperglycemia and diabetes. Clin Diabetes. 2011;29(1):3-9.

[30] Lazar HL. Glycemic Control during Coronary Artery Bypass Graft Surgery. ISRN Cardiol. 2012;2012:1-14.

[31] Peng L, Smiley D, Newton C, Pasquel F, Fereira ME, Umpierrez G. Risk Factors for Inpatient Hypoglycemia during Subcutaneous Insulin. J Diabetes Sci Technol. 2012;6(5):1022-9.

[32] Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, et al. American Association of Clinical Endocrinologists And American College of Endocriniology Position Statement On The Association Of SGLT-2 Inhibitors And Diabetic Ketoacidosis. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2016 Jun;22(6):753-62.

[33] Standards of medical care in diabetes—2015 abridged for primary care providers. Clin Diabetes. 2015 Apr;33(2):97-111.

[34] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes Care. 2015;38(1): 140-9.

[35] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

[36] Care H, Standards D. Diabetes care in the hospital. Diabetes Care. 2017;40(January):S120-7.

[37] Magalhães FO, Gouveia LMB, Torquato MTCG, Paccola GMGF, Piccinato CE, Foss MC. Metformin increases blood flow and forearm glucose uptake in a group of non-obese type 2 diabetes patients. Horm Metab Res = Horm und Stoffwechselforsch = Horm Metab. 2006 Aug;38(8): 513-7.

[38] Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1996 Nov;81(11):4059-67.

[39] Kamenova P, Atanasova I, Kirilov G. Metformin Improves Insulin Secretion and Reduces Insulin Resistance in People at High Risk for Development of Type 2 Diabetes Mellitus and Cardiovascular Disease. 2016;4(3):152-61.

[40] Panahi Y, Mojtahedzadeh M, Zekeri N, Beiraghdar F, Khajavi MR, Ahmadi A. Metformin treatment in hyperglycemic critically ill patients: Another challenge on the control of adverse outcomes. Iran J Pharm Res. 2011;10(4):913-9.

[41] An H, He L. Current understanding of metformin effect on the control of hyperglycemia in diabetes. J Endocrinol. 2016;228(3):R97-106.

[42] Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012 Mar;122(6):253-70.

[43] Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol [Internet]. 2012;13(4):251-62. Available from: https://doi.org/10.1038/nrm3311

[44] Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Review Metformin : From Mechanisms of Action to Therapies. Cell Metab [Internet]. 2014;20(6):953-66. Available from: http://dx.doi.org/10.1016/j.cmet.2014.09.018

[45] El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem. 2000;275(1): 223-8.

[46] Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J [Internet]. 2000 Jun 7;348(3):607-14. Available from: https://doi.org/10.1042/bj3480607

[47] Duca FA, Côté CD, Rasmussen BA, Zadeh-Tahmasebi M, Rutter GA, Filippi BM, et al. Metformin activates a duodenal Ampk–dependent pathway to lower hepatic glucose production in rats. Nat Med [Internet]. 2015;21(5):506-11.

Available from: https://doi.org/10.1038/nm.3787

[48] Christ-crain M, Kola B, Lolli F, Fekete C, Seboek D, Feltrin D, et al. AMP-activated protein kinase mediates glucocorticoid- induced metabolic changes : a novel mechanism in Cushing' s syndrome. 22(6):1672-83.

[49] Nader N, Sin S, Ng M, Lambrou GI, Pervanidou P, Wang Y, et al. AMPK Regulates Metabolic Actions of Glucocorticoids by Phosphorylating the Glucocorticoid Receptor through p38 MAPK. 2018;24(September 2010): 1748-64.

[50] Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature. 2013 Feb;494(7436):256-60.

[51] Diabetes T, Program P. Prevention or delay of type 2 diabetes. Diabetes Care. 2017;40(January):S44-7.

[52] Karlsson HKR, Hällsten K, Björnholm M, Tsuchida H, Chibalin AY, Virtanen KA, et al. Effects of metformin and rosiglitazone treatment on insulin signaling and glucose uptake in patients with newly diagnosed type 2 diabetes: A randomized controlled study. Diabetes. 2005;54(5):1459-67.

[53] Bostrom B, Uppal P, Chu J, Messinger Y, Gandrud L, McEvoy R. Safety and efficacy of metformin for therapy-induced hyperglycemia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35(7):504-8.

[54] Seelig E, Meyer S, Timper K, Nigro N, Bally M, Pernicova I, et al. Metformin prevents metabolic side effects during systemic glucocorticoid treatment. Eur J Endocrinol. 2017 Mar;176(3):349-58.

[55] Garber MD AJ, PhD, Duncan MD TG, Goodman MD AM, Mills RN DJ, BSN, et al. Efficacy of Metformin in Type II Diabetes. Am J Med [Internet]. 2018 Feb 6;103(6):491-7. Available from: http://dx.doi.org/10.1016/S0002-9343(97)00254-4

[56] Sr S, Greyber E, Ga P, Ee S. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus (Review). 2010;(4).

[57] Nye HJ, Herrington WG. Metformin: The safest hypoglycaemic agent in chronic kidney disease? Nephron-Clin Pract. 2011;118(4):380-3.

[58] Pilmore HL. Review: Metformin: Potential benefits and use in chronic kidney disease. Nephrology. 2010;15(4): 412-8.

[59] Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011;34(6):1431-7.

[60] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the european association for the study of diabetes (EASD). Diabetes Care. 2018;41(12):2669-701.

[61] Strack T. Metformin: a review. Drugs Today (Barc). 2008 Apr;44(4):303-14.

[62] Diabetes N, Clearinghouse I. Diabetes Prevention Program (DPP).

[63] Björkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. J Psychopharmacol. 2011 Mar;25(3):299-305.

[64] Temprosa M. Long-term effects of metformin on diabetes prevention:

Identification of subgroups that benefited most in the diabetes prevention program and diabetes prevention program outcomes study. Diabetes Care. 2019;42(4):601-8.

[65] Knowler WC, Barret-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. N Engl J Med [Internet]. 2002;346(6):393-403. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa012512