REVIEW

Emerging Concepts in Metformin Therapy: Hyperglycaemia and Beyond

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Abstract
Metformin has been extensively used in the management of type 2 diabetes mellitus (T2DM). A number of properties combined, including cost effectiveness, safety, weight neutrality, low risk of Hypoglycemia and cardiovascular protection moved metformin to the forefront of diabetes management and is now accepted as the standard first line therapy. Although other classes of glucose lowering medications were introduced to clinical practice in the recent times, none of such therapies has as yet demonstrated superiority to metformin to justify being considered as a first line therapeutic option. The use of metformin has extended in the last 2 decades to include diabetes prevention, gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS). There is accumulating evidence from observational studies to suggest a possible role for metformin in cancer prevention and in the management of non-alcoholic fatty liver disease. We reviewed the role of metformin in the prevention and treatment of T2DM and allied metabolic disorders and examined the non-glycaemic effects of metformin. In addition, we reviewed safety aspects pertinent to the usage of metformin in special clinical settings.

Keywords: Metformin, type 2 diabetes, Insulin resistance, Cardiovascular protection, Cancer, Gastrointestinal intolerability, Lactic acidosis, Gestational diabeted mellitus.

Introduction

Metformin is among a few medications which enjoyed long-term wide acceptance owing to its favourable glycaemic effects and safety alike. It is ranked among the top 10 generic drug prescriptions in the United States in 2009 with more than 42 million prescriptions (1). It belongs to the biguanide group of medications, the other being phenformin which was withdrawn from use because of serious adverse effects (2, 3). Although metformin use spanned many decades, its defined role in cardiovascular protection only came to light

in United Kingdom Prospective Diabetes (UKPDS) Study (4). Subsequent to the UKPDS observations, diabetes management guidelines almost unanimously recommended the use of metformin as the first line therapy for T2DM) (5-7). In this review, efficacy and safety of metformin will be discussed and emerging evidence regarding its use in glycaemic and non-glycaemic settings will be reviewed.

Mechanisms of action and efficacy of metformin

The effect of metformin on glucose is mediated by improving insulin sensitivity in liver, muscle and fat. Conventionally, metformin is known to reduce glucose concentration through reduction in glucose liver output brought about primarily by reducing the rate of gluconeogenesis and to a lesser extent by reducing glycogenolysis (8). Metformin also augments peripheral glucose utilization in muscle and fat (9,10). More recently, by mechanisms other than dipeptidyl-peptidase-4 (DPP-4) inhibition (11), metformin was shown to increase the level of glucagon-like-peptide-1 (GLP-1) (12). This mechanism of action may explain at least in part some of the metabolic effects of metformin, including weight neutrality and provides a unique advantage when metformin is combined with DPP-4 inhibitors through further enhancement of the incretin axis, which in turn offers the potential for additive glycaemic improvement (13,14).

Metformin for the treatment of T2DM and GDM

Metformin therapy for T2DM

Metformin has a number of attractive properties including weight neutrality, no hypoglycaemic reactions and cost-effectiveness making it the first line therapy in subjects with T2DM (5-7, 15). Treatment with metformin can be initiated at diagnosis in patients who have glycosylated haemoglobins (HbA1c) above 7.5% who are unlikely to be motivated enough to implement lifestyle measures whilst patients with HbA1c <7.5% who are motivated can be offered a 3 month trial of diet and exercise before a decision contemplating initiation of metformin therapies made (7). The glucose lowering efficacy of metformin is dose dependent (16). In addition, the magnitude of HbA1c lowering is dependent on the baseline level with greater lowering being observed in those with higher pre-treatment HbA1c (17). A recent meta-analysis of 35 trials of at least 12 weeks duration quantified the effects of metformin treatment (Figure 1) (18).

Metformin monotherapy reduced HbA1c by 1.12%, and metformin in combination with other oral glucose lowering therapies or insulin reduced HbA1c by 0.95% and 0.83%, respectively, with the effect being sustained at 24 weeks. In this analysis, the improvement in glycaemic control when metformin was combined with insulin was observed when the treatment protocol allowed for insulin dose adjustment in both metformin treated and untreated arms, which signifies a primary role for metformin in glucose lowering in insulin treated patients. Based on the established evidence, treatment with metformin is advocated at all stages of disease progression and the benefit is observed in both obese and non-obese subjects (19,20). However, metformin should be discontinued if absolute contraindications such as advanced renal disease or decompensated heart failure exist as detailed later.

Metformin in GDM

In general, metformin is an appealing therapy and a logical option in pregnancy because of ease of administration and cost effectiveness. Metformin use during pregnancy was found to provide adequate glucose control, less weight gain and lower rates of neonatal Hypoglycemia (21). Evidence from observational studies suggests that babies exposed to metformin in utero exhibited no adverse sequelae in the short term (22,23). Furthermore, smaller randomized studies also supported the notion of Metformin use in pregnancy (24). However, metformin crosses the placenta; therefore the possibility of a delayed or long term risk to babies born to mothers who were treated with metformin during pregnancy cannot be fully ruled out (23). For instance, a recent study reported potential harmful effect of metformin on the development of the fetal testis (25). These observations raise some concern about metformin safety during gestation.

Based on available evidence, some learned societies endorsed the use of metformin in pregnancy. Both the National Institute of Clinical Excellence (NICE) and Canadian Diabetes Association (CDA) include metformin as a therapeutic option in subjects with GDM (26,27). However, other societies such as the American Diabetes Association (ADA) and International Diabetes Federation (IDF) do not make similar recommendations perhaps a reflection of paucity of long term safety data (28,29).

Metformin use in children and adolescents

Metformin in obese children and adolescents without Diabetes

A number of clinical trials explored the short term role of metformin in the treatment of obesity and insulin

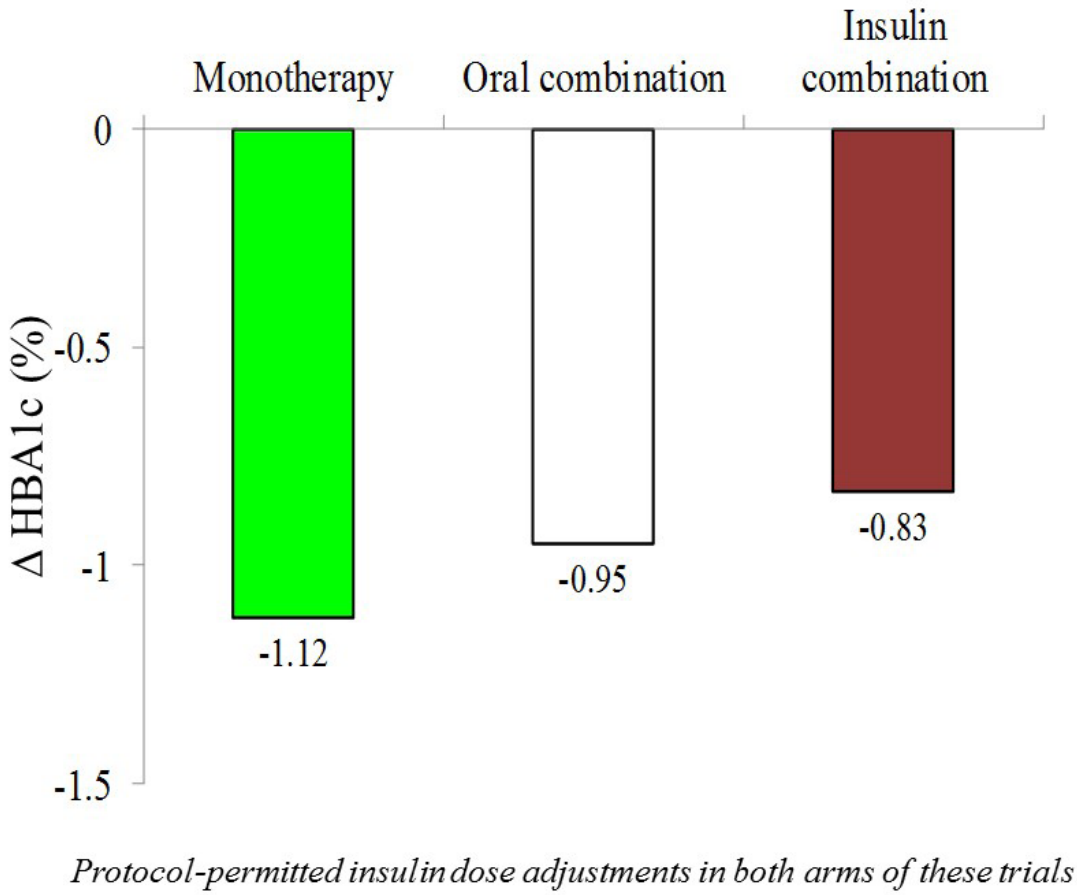

Figure 1. Magnitude of HBA1c lowering with metformin monotherapy, add-on to oral therapy or add-on to insulin: meta-analysis of 35 Trials of at least 12 weeks duration (18)

insensitivity in adolescents and reported modest weight loss with beneficial effects on insulin resistance and associated metabolic abnormalities (30-32). Although in the short-term, the effects of metformin on obesity and related metabolic abnormalities were encouraging, it's unlikely that this effect is maintained in the long term. Furthermore, positive effects of metformin should not take away the importance of lifestyle as the primary means of preventing the epidemics of obesity in this age group. Based on current evidence, metformin cannot be advocated as a therapeutic option in treating obese children and adolescents. Long term and larger studies may help to define a more precise role for metformin in treating metabolically abnormal and diabetes prone obese adolescents.

Metformin in adolescents with T2DM

IDF Guidelines for the management of T2DM in children and adolescents recommended lifestyle as the initial intervention in this group of patients. This is at variance with the most recently published guidelines by the American Academy of Pediatrics (33), American Diabetes Association and other societies which advocate the use of metformin at diagnosis. Although the guidelines acknowledged the importance of lifestyle, the rationale behind commencing metformin at diagnosis was based on the high failure rate of lifestyle measures with fewer than 10 % of adolescents with T2DM subjects achieving glycaemic targets through lifestyle alone. Furthermore, even when metformin therapy is instituted at diagnosis, the glycaemic effect is unlikely to be durable. The recently reported TODAY Trial (Treatment Options for Type 2 Diabetes in Adolescents and Youth) showed that most adolescents with T2DM do not sustain glycemic control with monotherapy and hence is the need for early addition of other glucose lowering agents

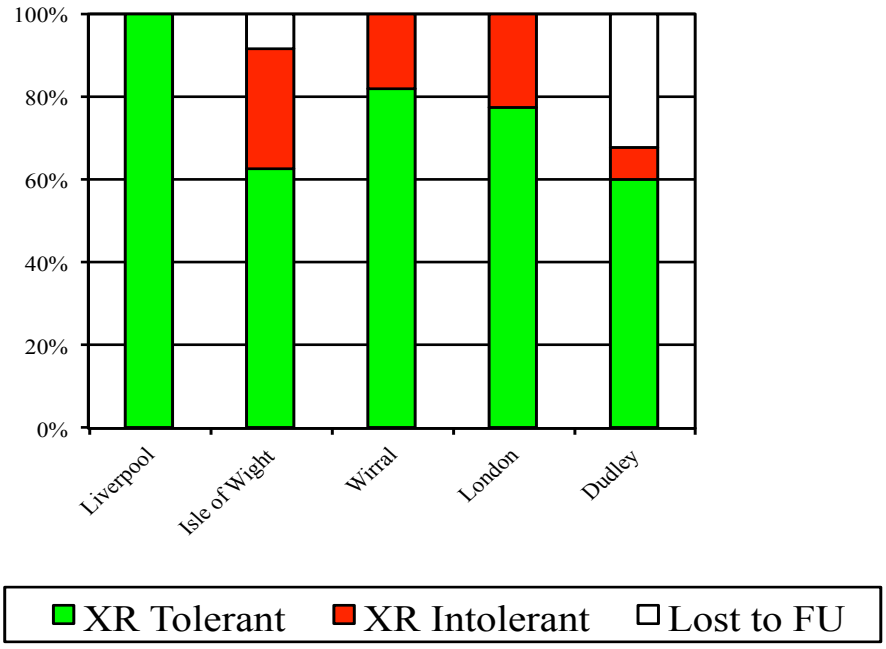

Figure 2. GI tolerability whilst on metformin XR in patients previously intolerant to immediate release formulation of metformin in five diabetes centers (36,37).

(34). Therefore, based on available evidence, early use of metformin is advocated in most adolescents with T2DM. However, from the safety respective and whilst non insulin therapies are more appealing to clinicians and patients alike, health care professionals involved in assessing and managing adolescents with assumed diagnosis T2DM should err on the side of caution by using insulin rather than metformin as the initial therapy if uncertainty exists about the nature of diabetes i.e. T1DM or T2DM.

Safety aspects of metformin therapy

Gastrointestinal (GI) intolerability and the role of extended release metformin

The commonest side effect of immediate release (IR) metformin is GI intolerability, with a range of symptoms including bloating, nausea, vomiting and diarrhoea. These side effects are generally brought about when patients are started on large doses of IR metformin or in the setting of rapid dose escalation. Dose reduction, administering IR metformin with or after meals and slow dose escalation tends to resolve or ameliorate GI side effects. However, approximately 5% of diabetic patients remain intolerant to the IR metformin even when cautious introduction and dose escalation principles are applied. The extended release (XR) formulation is an alternative form of metformin which possesses slower absorption characteristics in the upper gastrointestinal tract thereby allowing for once-daily dosing. XR Metformin has similar metabolic efficacy to the IR formulation and provides similar HbA1c lowering (35). In a study of 63 patients intolerant to IR metformin, 89% of these patients were able to tolerate XR metformin without experiencing GI side effects (figure 2) (36).

Table 1. Suggested use of metformin in patients with chronic kidney disease according to stages of kidney disease

CKD Stage	eGFR (ml/min/1.73 m^2)	Metformin Dose	Precautions and frequency of renal function monitoring
1	≥90	Maximum dose[1]	Annual[2, 3]
2	60-89	Maximum dose[1]	Annual[2, 3]
3a	45-59	Maximum dose[1]	3-6 months[2,3]
3b	30-44	Half the maximum dose	Every 3 months[2,3] Avoid if unexpected change in eGFR is anticipated,e.g unstable heart failure, diuretic use or other medications which may affect eGFR
4	15-29	None	
5	<15	None	

1. Maximum dose of metformin is generally 2000 mg per day
2. Apply standard precautions including withholding metformin therapy during episodes of dehydration, e.g. vomiting, gastroenteritis and before administration of contrast media.
3. More frequent monitoring can be applied as dictated by clinical setting.

Similar improvement in GI tolerability was reported by other investigators when subjects were switched from IR to XR metformin (37) (Figure 2). Therefore, in patients experiencing persistent GI side effects with IR Metformin, the XR formulation can be offered as an alternative therapeutic option.

Metformin in chronic kidney disease (CKD)

Metformin is eliminated renally, and rare incidents of lactic acidosis have been described in CKD patients (38). Based on the widely held view that metformin plays a causative role in precipitating lactic acidosis when the kidney function is deranged, restriction on its use was suggested. The food and drug administration in the USA recommended stopping metformin in men and women with serum creatinine concentrations >1.5 and >1.4 mg/dL (>132 and >123 μmol/L), respectively. However, the notion that metformin contributes to lactic acidosis has been challenged. Large meta-analysis and prospective observational studies showed no link between metformin and lactic acidosis in patients with CKD stage 3 (39,40). Clinical studies showed that the risk of lactic acidosis is similar among metformin and non-metformin users. Furthermore, smaller experimental data suggested no increase in lactic acidosis risk when metformin is used in patients with stable creatinine clearances as low as 20 ml/min/1.73 m^2 (41). On grounds of the reassuring evidence, recent recommendations support metformin dose reduction when creatinine clearance falls below 45 ml/min/1.73 m^2 and stopping metformin when creatinine clearance drops to less than 30 ml/min/1.73 m^2 (42,5). Caution should however be applied in avoiding use of metformin if kidney function is fluctuating and when the possibility of acute or sudden decline in kidney function is anticipated. Other safety measures worthy highlighting include stopping metformin before contrast media administration. Principles of good medical care dictate provision of routine advice to patients regarding with-holding metformin during episodes of dehydration such as with vomiting or gastroenteritis Suggested guidance on the use of metformin in CKD is summarised in table 1.

Metformin in heart failure

Patients with diabetes are at least twice as likely to develop

heart failure (HF) than patients without diabetes (43). Historically, the concern about the use of metformin in diabetic patients with HF has stemmed from the possible risk of precipitating the potentially fatal complication of lactic acidosis. On those grounds, many diabetes guidelines included HF as an absolute contraindication to metformin therapy. However, studies did not confirm the link between metformin use and lactic acidosis (39). A large recent meta-analysis of 34,504 patients with diabetes and HF concluded that metformin was as safe as other glucose lowering therapies even in those with reduced left ventricular ejection fraction or concomitant CKD (44). Observational study of 10,920 patients in Denmark reported lower mortality in the group of diabetic patients with HF who were treated with metformin compared to treatment with a sulfonylurea or insulin (45). Similar observations were made in a study of 6185 patients with HF and diabetes, where patients treated with metformin had lower rates of mortality at 2 years of follow up (46). The survival benefit was observed across different subgroups of HF, including those with renal insufficiency.

The recently published 2013 ADA guidelines understandably erred on the side of safety by adopting a conservative approach whereby metformin was recommended as a viable option in stable HF if renal function is normal (6). Based on the reassuring evidence that HF patients on metformin fare as well if not better than other glucose lowering therapies, the Canadian Diabetes Association recommends metformin as first line therapy in HF patients with mild to moderate renal dysfunction (27).

Metformin and deficiency of vitamins

In T2DM, exposure to metformin has been linked to reduced B12 absorption and the development of biochemical vitamin B12 deficiency. The risk of developing B12 deficiency has been associated with the duration of metformin use (47) and the dose employed (48). On the whole, approximately a quarter of patients on metformin therapy develop a variable degree of B12 deficiency (49). However, whilst classical B12 deficiency presents with clinical symptoms including anaemia, peripheral neuropathy, cognitive dysfunction and depression, not all people with biochemical vitamin B12 deficiency will develop clinical symptoms (50). Presently, there is no evidence to justify routine screening for B12 deficiency as the cost-effectiveness of mass screening and the benefit of treating subclinical deficiency are at best unproven, nonetheless, it is prudent to adopt a targeted screening for those at a particular risk of developing B12 deficiency including patients on long-term high dose metformin therapy especially in the setting of neuropathy, cognitive dysfunction and anaemia. The American Diabetes Association and others recommend checking B12 status in subjects with severe neuropathy especially in those taking metformin for prolonged periods (6,51). Patients with proven B12 deficiency should be treated. Route of B12 administration is a contentious issue. Oral B12 therapy can be effective in correcting B12 deficiency (52,53). It was pointed out that the amount of vitamin B12 included in most of the multivitamins preparations (6 μg) is not adequate to correct existing deficiency (54) and a higher dose of oral B12 (1000 mcg per day) was advocated (55). The other widely accepted form of B12 supplementation is the intramuscular injection which leads to more speedy correction of existing deficiency (56,57).

Metformin use in disease prevention

The preventative use of metformin covers three areas namely prevention of T2DM in high risk groups, cardiovascular protection and prevention of cancer.

Metformin for the prevention of T2DM

The US Diabetes Prevention Program (DPP) demonstrated that metformin reduces the risk of progression of impaired glucose tolerance (IGT) to diabetes by approximately 31%. This beneficial effect of metformin was mainly observed in subjects with body mass index (BMI) > 35 kg/m^2 and younger than 60 years of age (58). Accordingly, metformin is recommended as a therapeutic option in subjects with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and those in whom the HbA1c level lies in the pre-diabetes range (5.7-6.4%) (6). In women with past history of GDM, subgroup analysis of the DPP suggested that metformin is associated with 50% risk reduction in progression to diabetes (59). Based on these observations, metformin as well as lifestyle are the tools currently available to prevent progression to diabetes in this group of patients (6). Whilst metformin is considered as a therapeutic option in subjects with pre-diabetes, lifestyle has been shown to be superior to Metformin in preventing diabetes. The DPP, the FINISH and the DaQing intervention trials explored the role of lifestyle intervention in subjects with pre-diabetes and reported a delay in the progression to diabetes of 34%, 38% and 43% at 10, 13 and 20 years respectively (58,60-62). Therefore, this mode of intervention should be explored before considering any pharmacological means. Those who fail life style can reasonably be commenced on metformin.

Cardiovascular outcomes

The primary objective of intervention in T2DM is the prevention of vascular disease. Whilst studies have confirmed that controlling hypertension and dyslipidemia were associated with significant reduction in cardiovascular complications (63-65), therapy aiming at controlling hyperglycemia did not reach similar conclusions (66-68). Limited data derived from the UKPDS and based on 342 patients initiated on metformin therapy suggested a role for metformin in the prevention of vascular disease and all cause mortality (4). A number of observational studies have suggested a cardio protective effect of metformin in patients with T2DM with high baseline CV risk (69,70). In a randomized, placebo controlled trial, Kooy et al, showed that when metformin was added to insulin, a reduction in macrovascular disease was observed (71). On the contrary, a recent meta-analysis of 13,110 patients did not support a role for metformin in reducing all cause and cardiovascular mortality (72). Differences in patients' characteristics and study design may conceivably explain the inconsistency in reporting metformin benefit. Furthermore, the observations made in this meta-analysis should not detract physicians from using metformin as the number one therapy of choice giving its long tract safety record and affordability. Ongoing CV outcome trials using newer diabetes medications may lead to the reappraisal of preferred therapy choices.

Metformin and cancer

Vascular complications are the leading cause of death in diabetes (73). With the improved control of vascular risk factors (74) we are witnessing the emergence of cancer as an important cause of morbidity and mortality in diabetes (73). Epidemiological data suggests that many types of cancer occur with a higher frequency in people with diabetes including cancer of the liver, pancreas, colon, breast, kidney, bladder, uterus and ovary (75,76). The precise aetiology for the observed increase in cancer risk in diabetes is not well understood, however a number of aetiological factors have been advanced including Hyperglycemia (77,78), hyperinsulinaemia (78) inflammation and oxidative stress (79). It is plausible that therapies which control such risk factors may potentially prove to posses anti-tumour properties. In this context, in the analysis of the DART study (Diabetes Audit and Research in Tayside Study) participants, potential benefit of metformin was first described by Evans et al (80) who reported a dose-dependent reduction in cancer risk. Numerous subsequent observational studies demonstrated a reduced risk of breast (81), Colonic (82) and liver cancers (83). Investigators in the ZODIAC (Zwolle Outpatient Diabetes Project Integrating Available Care) study made two observations: first, patients with T2DM are at a greater risk of cancer, and second, metformin users had lower cancer mortality compared with nonusers (84). Whilst the observational data hints to an important role for metformin as an anti-cancer agent, causal association whereby metformin directly lowers cancer risk cannot be proven. The possibility always exists that observational data can suffer from the effect of unmeasured confounders which in turn may lead to erroneous and misleading results. Therefore, while the perceived effect of metformin on cancer risk is reassuring, drawing firm conclusion on the effect of metformin on cancer requires the conduction of prospective randomized studies. In the meantime, metformin will continue to retain pole position thanks to its long track record as one of the most efficacious, safest and least expensive diabetes therapy.

Miscellaneous Issues

Finally, three remaining topical issues will be discussed, these are the role of metformin in PCOS, the potential use of metformin in nonalcoholic fatty liver disease (NAFLD) in adults and adolescents and the safety of metformin use by breast feeding mothers.

Metformin in PCOS

PCOS is by far the commonest condition that leads to ovulatory failure. Underlying abnormalities playing a role in the pathogenesis of PCOS include luteinizing hormone hypersecretion (85), primary adrenal and ovarian abnormalities (86-88) and insulin resistance which is out of proportion to what is predicted from the prevailing BMI (89). Given that insulin resistance is common in PCOS and that the severity of this disorder is directly correlated with the degree of insulin resistance (90, 91), it makes sense to explore the therapeutic advantages of medications with insulin sensitising properties. From the reproductive prospective, anovulatory women with PCOS seeking fertility should be offered clomiphene citrate therapy along with lifestyle as the preferred ovulatory induction option. If reduced multiparity is deemed a necessity, metformin can be considered as an alternative first line agent for ovulation induction (92,93). The use of metformin as a first line therapy for ovulation induction can also be considered in anovulatory women with BMI<30 (94).

Metformin in NAFLD in adults and adolescents

NAFLD is a disorder which encompasses a spectrum

of fatty liver disorders ranging from fatty liver at one end to steatohepatitis and cirrhosis at the other end in the absence of excessive alcohol consumption. The risk of NAFLD in diabetes has been reported to be as high as 70%. In the setting of T2DM, patients with NAFLD are more likely to develop more advanced liver disease associated with fibrosis, cirrhosis and in some instances hepatocelluar carcinoma. Therefore, early diagnosis of NAFLD is important in allowing for instituting timely intervention aiming at not only prevention of liver disease progression but also to recognize patients at higher risk for cardiovascular disease who warrant early intervention (95). Studies using metformin in treatment of NAFLD have demonstrated improvement in liver enzymes, however, not all trials showed an improvement in liver histology (96-101). Studies of 6 months duration using metformin up to 1.7 gm/day failed to demonstrate regression in histological abnormalities (98). On the other hand, longer duration trials spanning 12 months and using a higher dose of metformin i.e. 2 grams/day showed histological improvement (102, 103). Furthermore, observational studies showed a reduction in the risk of developing Hepatocellular carcinoma (HCC) and all liver cancers in subset of patients exposed to metformin treatment (82). Based on the existing evidence, larger long term randomized studies are required to establish the role of metformin in treating NAFLD. In the absence of such an evidence, and based on the encouraging results from smaller studies, metformin should be considered as an adjunct therapy to lifestyle and weight reduction in NAFLD associated with diabetes.

Metformin and breast feeding

Few studies looked at the safety of metformin during lactation. A study of five nursing mothers by Hale et al. showed that infants' exposure to metformin was only 0.28% of the weight- normalized maternal dose and considered this value to be well below the 10% level of concern in breast feeding (104, 105). Similar observations were made by Briggs et al. who also showed that infants' exposure to metformin was below 1% of the maternal weight – adjusted dose and such a small exposure led to no decline in blood glucose level in the 3 studied infants (106). In another small study of 3 nursing mothers, Gardiner et al. made the observation that there was a steady level of metformin concentration in the breast milk implying that the time of metformin ingestion by the mother has no bearing on the amount of metformin detected in breast milk (107). In a relatively larger study looking at growth, motor and social development, Glueck et al. observed no differences in outcomes between breast- and formula-fed infants at 3 and 6 months of age (108). Based on no demonstrable adverse signals, the NICE Guidelines suggest that women with pre-existing T2DM who are breastfeeding can resume or continue to take metformin. The guidelines also recommend obtaining an informed consent on the use of metformin during lactation, a practice which is probably not widely implemented by clinicians (26). In summary, although metformin appears to be safe during lactation, randomized prospective longer term trials will help in drawing a more robust conclusion.

Metformin in non diabetic obesity

Most of the studies examining the role of metformin in primary obesity were of short duration and included small number of patients. Some of these studies reported meaningful weight loss which is comparable to what is achieved with the use of established anti-obesity medications (109-111). The net weight loss reported in other studies was not different from placebo, perhaps a reflection of study design and/or patients population (112). Long-term large randomised trials exploring the use of metformin in obesity are lacking. Therefore the totality of available evidence does not support a definitive role for metformin in the treatment of primary obesity (110-115).

Final remarks and conclusions

Metabolic and cardiovascular properties of metformin are undisputed, hence is the unanimous endorsement by all diabetes societies and guidelines in recommending metformin as the first therapy of choice in subjects with T2DM. Established safety of metformin in mild to moderate CKD, in stable heart failure and the availability of slow release formulation of metformin allowed for wider use of this product in special settings. Use of metformin has extended recently to encompass other entities including pre-diabetes, GDM and PCOS. Encouraging evidence, albeit limited, suggests a possible favourable effect of metformin in cancer, NAFLD, and obesity. Whether randomised trials confirm this perceived benefit remains to be ascertained.

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