Metformin Use in Adolescents: Old and New Therapeutic Perspectives

Fawziya Alkhalaf[1,2], Ashraf T Soliman[2,3]*, and Vincenzo De Sanctis[4]

[1]Pediatric Department, HMC, Doha-Qatar
[2]Department of Pediatrics, Weill Cornell Medical College-Doha-Qatar
[3]Department of Pediatrics, Division of Endocrinology, Alexandria University Children's Hospital Alexandria, Egypt
[4]Department of Pediatrics and Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy

Abstract

Metformin (dimethylbiguanide) is now considered to be the most widely prescribed agent in the treatment of diabetes. The global increase in the prevalence of obesity among children and adolescents is accompanied by the appearance and increasing prevalence of insulin resistance, prediabetes and type 2 diabetes mellitus (T2DM). In addition, children and adolescents with premature pubarche and polycystic ovary have considerable degree of insulin resistance. The insulin sensitizing action/s of Metformin encourage (add s to encourage to be encourages) many investigators and physician to use it as the primary drug of choice in these conditions for both prevention and treatment. However, long term controlled studies are still required to assess the degree and duration of effectiveness and safety of using Metformin .In this review the old and new therapeutic perspectives of this drug are presented.

Keywords: Metformin; Adolescents; Obesity; T2 DM; Prediabetes; Insulin resistance; PCOs

Introduction

Metformin (1,1-dimethylbiguanide) is the most widely used drug to treat type 2 diabetes, and is one of only two oral antidiabetic drugs on the World Health Organization (WHO) list of essential medicines [1]. Its history can be traced back to the use of Galega officinalis as a herbal medicine in medieval Europe. Its name derives from gale (milk) and ega (to bring on), as Galega has been used as a galactogogue in small domestic animals (hence the name "Goat's rue"). Studies in the late 1800s indicated that Galega officinalis was rich in guanidine and in 1918 guanidine was shown to possess hypoglycaemic activity in animals. Jean Sterne was the first to investigate dimethylbiguanide (Metformin) for clinical development and proposed the name 'Glucophage' (glucose eater) and published his results in 1957 [2-4].

Metformin is the most widely prescribed drug to treat hyperglycemia in individuals with T2DM and is recommended, in conjunction with lifestyle modification (diet, weight control and physical activity), as a first line oral therapy in the recent guidelines of the American Diabetes Association and European Association of the Study of Diabetes. It is effective anti-hyperglycaemic agent that inhibits hepatic glucose production and increases peripheral glucose uptake. Metformin also exerts beneficial effects on circulating lipids and exhibits cardio-protective features in obese patients. Clinical trials suggest that Metformin, that is effective in treating T2DM, may also have therapeutic potential in other conditions in which insulin resistance constitutes part of the pathogenesis, including obesity, prediabetes, polycystic ovary disease, non-alcoholics fatty liver and premature pubarche (Figure 1). Epidemiological studies have shown a decrease in cancer incidence in Metformin-treated patients, suggesting a potential application of the drug as an anti-cancer agent [5].

Mechanism of Action

Although prescribed and used extensively since the end of the precise molecular (or biochemical) mechanism/s of action remain incompletely understood. It acts by countering insulin resistance, particularly in liver and skeletal muscle. It suppresses hepatic gluconeogenesis, increases peripheral insulin sensitivity in insulin sensitive tissues such as muscle and adipose tissue, and enhances peripheral glucose utilization [6-9].

Figure 1: Insulin resistance (IR) and organ dysfunction.
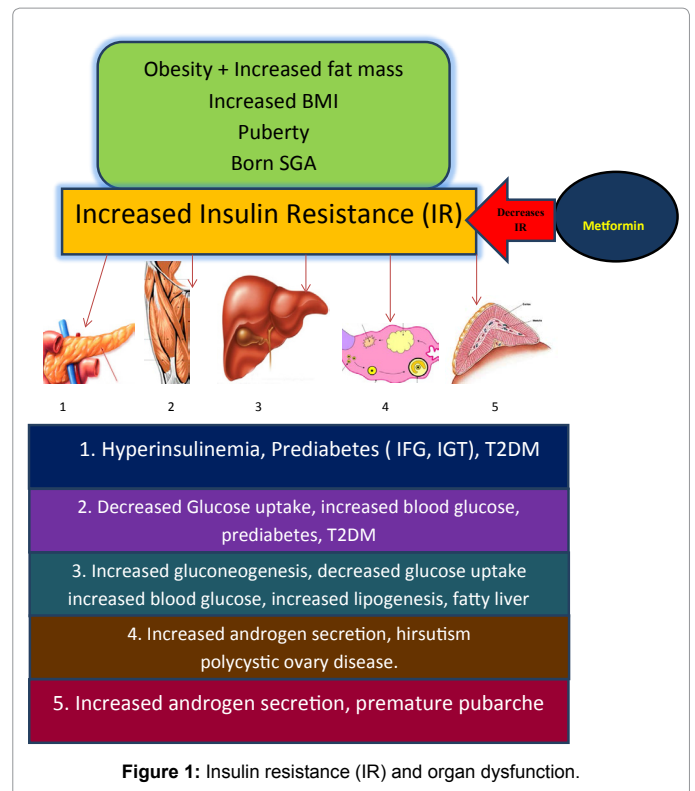
*Corresponding author: Ashraf Soliman, Professor of Pediatrics and Endocrinology, Department of Pediatric Hamad Medical Center (HMC), Doha - Qatar. (*) HMC, Qatar, Tel: +974-55983874; E-mail: atsoliman@yahoo.com

However, the main effect of Metformin appears to be decreasing hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex 1. This transient decrease in cellular energy status promotes activation of adenosine monophosphate-activated protein (AMPK), a well-known cellular energetic sensor. AMPK is a protein kinase ubiquitously expressed in mammalian tissues and involved in regulating energy balance. Activation of AMPK stimulates adenosine triphosphate (ATP)-producing catabolic pathways, while inhibiting ATP-consuming anabolic pathways, thereby, maintaining cellular energy stores. In skeletal muscle, activation of AMPK increases glucose uptake and lipid oxidation. In adipose tissue, activation of AMPK reduces both lipolysis and lipogenesis [6-9]. Metformin regulates glucose transporter 4 (GLUT4) translocation through AMP-activated Protein Kinase (AMPK)-mediated Cbl/CAP Signaling. It enhances insulin signaling in insulin-dependent and -independent pathways [10]. In the liver, activation of AMPK inhibits gluconeogenesis and lipid synthesis but increases lipid oxidation. The activated AMPK decreases flux of free fatty acids and inhibits lipolysis, which may indirectly improve insulin sensitivity through reduced lipotoxicity (reduces hepatic lipogenesis) and exert an indirect effect on hepatic insulin sensitivity to control hepatic glucose output. In the heart, Metformin increases fatty acids uptake and oxidation, and increases glucose uptake and glycolysis [9-14]. Metformin can also antagonize the action of glucagon, thus reducing fasting glucose levels [15]. In summary, activation of AMPK in skeletal muscle, liver and adipose tissue decreases circulating glucose, lipids, reduces fat accumulation and enhances insulin sensitivity.

Additional action of Metformin action is through induction of a profound shift in the faecal microbial community profile in diabetic mice and it has also been proposed that this may contribute to its mode of action possibly through an effect on Glucagon-like peptide-1 (GLP-1) secretion [16,17]. Moreover, Metformin enhances the expression of the genes encoding the receptors for both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) in mouse islets and also increases the effects of GIP and GLP-1 on insulin secretion from beta cells. These incretin-sensitising effects of Metformin appear to be mediated by a peroxisome proliferator-activated receptor α-dependent pathway, as opposed to the more commonly ascribed pathway of Metformin action involving AMP-activated protein kinase [18].
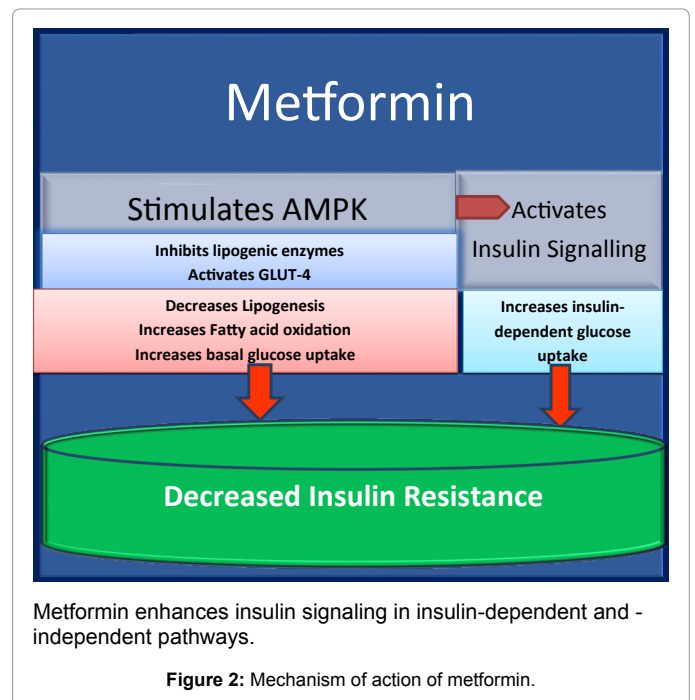
The protective effect on the cardiovascular system cannot be fully explained by its blood glucose-lowering properties. These effects may be partly mediated via beneficial effects on circulating markers of endothelial function (vascular cell adhesion molecule-1 [VCAM-1], E-selectin), fibrinolysis (plasminogen activator inhibitor-1 [PAI-1]) and chronic inflammation (C-reactive protein [CRP]) [19,20].

These mechanisms work together to reduce the levels of circulating glucose, increase insulin sensitivity, and reduce the hyperinsulinemia associated with insulin resistance [6-20] (Figure 2).

Pharmacological Properties of Metformin

Metformin has a half-life of around five hours and undergoes renal excretion with 90% being eliminated within 24 hours. It can be prescribed as 500 mg or 850 mg tablets. In adults , it can be started at the 500 mg dose and increased in weekly increments until the maximum tolerated dose is achieved, normally 2 g/day [21,22].

The intestinal absorption of Metformin may be primarily mediated by plasma membrane monoamine transporter (PMAT/SLC29A4), which is expressed on the luminal side of the enterocytes. Metformin

Metformin enhances insulin signaling in insulin-dependent and -independent pathways.

Figure 2: Mechanism of action of metformin.

has an oral bioavailability of 50-60% under fasting conditions, and is absorbed slowly. Peak plasma concentrations (C_{max}) are reached within one to three hours of taking immediate-release Metformin and four to eight hours with extended-release formulations. Steady state is usually reached in one or two days. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately a 40% lower mean peak plasma concentration. The plasma protein binding of Metformin is negligible. It should be taken with food to reduce the potential for gastrointestinal side effects. Metformin is undetectable in blood plasma within 24 hours of a single oral dose [21,22]. After administration of a single oral Metformin HCl 500 mg tablet with food, geometric mean Metformin Cmax and AUC did not differ between adolescents with T2DM (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age) [23].

Side-effects and Contraindications of Metformin

Gastrointestinal upsets are the main complain associated with Metformin use. However the main side effect of alarm is its association with lactic acidosis particularly in the setting of renal and cardiac impairment. Lactic acidosis associated with Metformin is a rare condition. No patient in the UKPDS study developed lactic acidosis. A systematic review of the risk of lactic acidosis with Metformin found no cases of fatal or non-fatal lactic acidosis in 274 comparative trials and cohort studies, and estimated that the upper limit of the true incidence of lactic acidosis per 100,000 patient years was 5.1 with Metformin and 5.8 without. Most cases of Metformin-associated lactic acidosis documented in the literature happen during periods of tissue hypoxia (myocardial infarction, acute left ventricular failure or septicaemia). The most common symptoms following overdose appear to include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and, rarely, hypoglycemia [24]. This gut irritating effect is believed to be mediated through inhibition of serotonin reuptake transporter (SERT)-mediated intestinal reuptake of serotonin resulting in increased intestinal motility and water retention [25].

Although 90% is renally excreted, accumulation is rare in the

absence of moderate-to-severe renal impairment. Members of the American Diabetes Association and European Association for the Study of Diabetes, report that Metformin seems safe unless eGFR falls to <30 mL/min per 1.73 m^2. The National Institute for Health and Clinical Excellence specifies that Metformin be stopped if serum creatinine exceeds 150 µmol/L (1.7 mg/dL) or eGFR is below 30 mL/min per 1.73 m^2. In contrast, the Canadian Diabetes Association practice guidelines recommend caution with eGFR <60 mL/min per 1.73 m^2 and contraindicating its use with eGFR <30 mL/min per 1.73 m^2 [26-28]. Therefore, Metformin should not be given to patients with severe renal impairment, hepatic disease, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials. Metformin should be temporarily discontinued during a gastrointestinal illness. Hypoglycemia is very uncommon with Metformin monotherapy but has been reported in combination regimens, likely due to Metformin potentiating other therapeutic agents [29].

Long-term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B12. Malabsorption of vitamin B12 occurs with metformin in 30% of diabetic subjects. The earliest manifestations are numbness and paresthesias in the feet, which, unless the vitamin B12 deficiency is corrected, can be followed by weakness, ataxia, sphincter disturbance, and changes in mental status. B12 deficiency –associated macrocytic anemia, is often preceded by the development of neuropathy. While the anemia of vitamin B12 deficiency is reversible, the progress of the neuropathy is only arrested and not reversed with initiation of vitamin B12 therapy [30].

Therapeutic Perspectives

Type 2 Diabetes Mellitus (T2DM)

Obesity has dramatically increased in prevalence world-wide among children and adolescents, accompanied by the appearance and increasing prevalence of type 2 diabetes mellitus (T2DM) [31]. Depending on geographic locations, T2DM accounted for 8-45% of new cases of childhood diabetes [32].

In the treatment of T2 DM in adolescents, Metformin is still the preferred first-line treatment to AAP clinical practice guidelines 2013 [33]. Metformin should be initiated for adolescents who present with mild hyperglycemia (random venous or plasma blood glucose concentrations <250 mg/dL) and HbA1c less than 9% at the time of diagnosis with a concomitant initiation of lifestyle modification program, including nutrition and physical activity [33].

Metformin has proved to be effective and safe with multiple metabolic and cardiovascular benefits. Metformin was approved in Canada in 1972, but did not receive approval by the U.S. Food and Drug Administration (FDA) for T2DMuntil 1994. Glucophage was the first branded formulation of Metformin to be marketed in the United States, beginning on 1995. It has been approved by the Food and Drug Administration (FDA) for children with T2DM aged 10 years and older [34].

The International Society of Pediatric Diabetes (ISPAD) recommended Metformin as the first drug to be used in children with T2DM because of its advantages over sulfonylureas. Metformin has lower risk of developing hypoglycemia, decreases or stabilizes the weight and decreases LDL-C and triglyceride level [35].

However recent data from the TODAY study (Treatment Options for T2DM in Adolescents and Youth) have showed some discouraging results because 52% of adolescents with recent-onset T2DM treated with Metformin alone manifested treatment failure within few years after diagnosis, implying that most youth with T2DM will require multiple oral agents or insulin therapy shortly after diagnosis [36].

Obesity, insulin resistance and prediabetes

Rates of childhood overweight and obesity have nearly tripled in the U.S. and western countries over the last 30 years. Concomitant with the rise in prevalence of childhood obesity there has been a corresponding increase in the incidence of cardiovascular risk factors, such as insulin resistance, prediabetes or impaired glucose tolerance (IGT), T2DM, hypertension, hyperlipidemia and non-alcoholic fatty liver disease (NAFLD) [34,37].

Lifestyle intervention is recommended as the primary treatment for childhood obesity. However, the long-term outcomes of lifestyle interventions for childhood obesity carried out in a clinical-practice setting have varied widely. Low rate of success in many trials promoted an interest in pharmacological interventions and bariatric surgery to prevent diabetes among obese children and adolescents [37].

According to many studies the major effect of Metformin may be through inhibition of appetite probably by increasing the levels of GLP-1 and by interacting with signaling of other hormones or cytokines (such as ghrelin, leptin and insulin) [33-35]. Reduction of excessive weight gain has a favorable effect on blood pressure, glycemic control and lipid metabolism [34,38-40].

Pediatric randomized, controlled trial studies have shown improvement in BMI, fasting serum glucose, fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR) and lipid profile in patients on Metformin therapy for exogenous obesity associated with insulin resistance [41,42]. A systemic review identified 14 randomized controlled trials (RCTs) of Metformin use in non-diabetic obese children and adolescent (aged <18 year) [39]. These RCTs involved a total of 946 children with mean ages from 10 to 16 years. Some included data on glycemic control and most of them involved some sort of lifestyle intervention in addition to the drug with variable follow-up periods. The overall analysis showed a small but significant net body mass index (BMI) reduction of 1.16 kg/m^2 attributable to the drug. Subgroup analysis showed a greater effect for those with a higher BMI at baseline and in younger patients [43].

Escalating doses of Metformin in low-dose (250 mg), intermediate-dose (500 mg), and high-dose (750 mg) treatment three times per day were administrated into normal 22 adults for a three-weeks treatment period. Metformin significantly reduced fasting plasma glucose and insulin resistance after receiving this treatment at therapeutic doses including low-dose (5%, 17%), intermediate-dose (6%, 25%) and high-dose treatment (6%, 21%). Also, serum cholesterol decreased significantly using Metformin at therapeutic doses including low-dose (4%), intermediate-dose (8%) and high-dose treatment (7%) [44]. In other studies, Metformin dose of 1 g daily appeared marginally less effective than 2 gm and with these doses adverse events were infrequent, and mostly gastrointestinal [42,43].

The 'lifestyle' interventions, which varied greatly between the studies, produced significant BMI reductions in most, and the added effect of Metformin was relatively small. In addition, the effect of Metformin was more apparent in those studies that lasted only 6 months compared to those that continued for a year or more, suggesting a decline in effectiveness over time. Certain ethnic groups and those patients with insulin resistance appeared to have a better benefit with the Metformin use [45-49].

The AACE suggests Metformin to be considered for younger patients who are at moderate to high risk for developing DM; for patients with additional CVD risk factors including hypertension, dyslipidemia, or polycystic ovarian syndrome; for patients with a family history of DM in a first-degree relative; and/or for patients who are obese [50].

In conclusion, Metformin offers significant potential to intervene to reduce or reverse the metabolic and endocrine changes associated with obesity during puberty. However, it appears that publication bias towards trials with positive outcomes has made Metformin appear more effective than it is. Although it is a valuable and useful drug for obese adolescents with insulin resistance but certainly it is not the answer to the obesity epidemic. Larger, long-term studies across different populations are needed to establish the role of Metformin as therapy for obesity and cardio-metabolic risk in young people.

Type 1 diabetes (T1DM) with insulin resistance

Insulin resistance of puberty is well documented in both non diabetic and diabetic adolescents. During puberty increased body fat and BMI correlate strongly with insulin resistance [51,52]. In adolescents with T1DM, it likely plays a role in complicating glycemic control and potentially increasing cardiovascular disease (CVD) risk [53].

In the Diabetes Control and Complications Trial (DCCT), adolescents achieved HbA1c levels that were on average 1% higher than in adults in both the conventional and intensive treatment groups, despite receiving more insulin (units per kilogram body weight) and having increased weight gain. This triad of high HbA1c, high insulin dosage, and weight gain suggests that the insulin administered was less effective in maintaining glycemic control (i.e., insulin resistance) in the adolescent cohort [54,55]. It is observed that although insulin dosages are often increased to overcome the resistance to insulin, the metabolic control often deteriorates during the later stages of pubertal development [56].

The addition of Metformin to insulin therapy in an attempt to improve insulin sensitivity, promote weight control, and reduce insulin dose requirements in patients with T1DM has been assessed in systematic reviews. One systematic review identified nine studies, including both adolescents and adults. The studies compared Metformin versus placebo or another comparator in parallel or crossover design for at least 1 week. Metformin use was associated with reduction in insulin-dose requirement (reductions in total daily insulin of 5.7-10.1 units/day), HbA1c (reductions of 0.6%-0.9%), weight (range of weight loss, 1.7-6.0 kg), and total cholesterol (reduction of 11.6-15.8 mg/dL). Formal estimates of combined effects were possible from five studies which found a significant reduction in insulin dose of 6.6 units/day [57].

Another systematic review compared metformin added to insulin vs insulin therapy alone. In 60 patients the authors found a reduction in HbA1c values when Metformin was added to insulin. One of the studies also showed a 10% decrease in insulin dosage among those taking Metformin. Hypoglycemia and gastrointestinal disturbances were among the most commonly occurring adverse effects of combination therapy [58].

A double blind placebo controlled study was conducted to assess the effects of Metformin on metabolic parameters when added to insulin therapy in 74 pubertal adolescents (ages: 13-20 yr) with T1DM [59]. Participants were randomized to receive either Metformin or placebo for 6 months. Compared to placebo group, Metformin caused

significant decrease in total daily insulin dose, BMI z-score and waist circumference at 3 and 6 months compared to baseline, even among normal-weight participants. In the placebo group, total insulin dose and systolic blood pressure increased significantly at 3 months and total insulin dose increased significantly at 6 months. No significant change was observed in HbA1c at any time point between Metformin and placebo groups or within either group [59].

The American Association of Clinical Endocrinologists (AACE) recommended the addition of Metformin and/or insulin in children or adolescents with T2DM when glycemic targets are not achievable with lifestyle measures alone [55].

In conclusion, Metformin is expected to help those overweight adolescence with T1DM who require large doses of insulin, and/or continue to have uncontrolled HbA1c (> 8%) values despite adherence to insulin. However, patients should be made aware that hypoglycemia may become more likely once Metformin is added to their insulin regimen [60].

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is recognized as the most common cause of liver disease in obese children and adolescents. NAFLD includes a wide spectrum of histologic abnormalities ranging from hepatic steatosis to non-alcoholic steato-hepatitis (NASH) that may progressto cirrhosis, and subsequent end stage liver disease and hepatocellular carcinoma [61-63].

The first-line treatment of NAFLD is currently based on diet and lifestyle modifications. Most of the published studies in NAFLD population have shown that gradual weight loss (5-10%), calorie-restricted diet, and regular physical exercise lead to a decrease in the incidence of metabolic syndrome, improvement in liver enzyme profile, and resolution of hepatic steatosis [64,65]. A pharmacological treatment in patients with NAFLD is not universally accepted yet. However, given that insulin resistance plays a key role in the pathogenesis of NAFLD, many studies have evaluated the use of insulin sensitizers (Metformin and Thiazolidinediones) as a possible treatment for this disease [66]. The potential role of Metformin has also been examined in pediatric patients with NAFLD. Results in pediatric population were similar to those of adults and supported the beneficial effects of Metformin on biochemistry liver profile [65-67]. Schwimmer et al. studied 10 obese children and adolescents (8–17 years) with biopsy-proven NASH and elevated alanine aminotransferase (ALT) level). The participant ingested Metformin (1 g/day) for a period of 24 weeks. Metformin caused a significant improvement in alanine aminotransferase (ALT) with a mean change of −86 U/L and normalization in 40% of patients, although weight loss was not achieved. Furthermore, Metformin was effective in reducing liver fat in 90% of subjects as assessed with magnetic resonance spectroscopy [65]. Nadeau et al. randomized fifty obese and insulin-resistant adolescents to receive lifestyle recommendations plus Metformin (850 mg twice a day for 6 months) or placebo. Treatment with Metformin resulted in significant decrease in serum aminotransferases level, liver fat, and increased insulin sensitivity compared with untreated or placebo-treated group [67]. Six open-label trials have evaluated the liver histology modification together with serum aminotransferase levels and insulin resistance markers' amelioration in NAFLD patients treated with Metformin (dose ranging from 1.4 g/day to 2.0 g/day and treatment duration varying from 24 to 48 weeks) alone or in association with other drugs. All these studies reported an improvement in the indices of insulin resistance: five studies reported a reduction in liver function test values and one reported a non-significant increase of these

values. In terms of histological improvement, only three trials showed significant differences in inflammation, steatosis, and fibrosis after treatment with Metformin [68-73].

A study evaluated the efficacy of the addiction of low dose of Metformin (500 mg twice a day) to dietary treatment (1300 kcal) in 50 obese and nondiabetic patients. Metformin plus dietary therapy was associated with an improvement or even disappearance of hepatic steatosis similar to what observed with diet treatment alone. Metformin treatment was also associated with increased insulin sensitivity and reduced fasting glucose than diet alone [74]. On the other hand, a randomized multicenter placebo controlled trial called the TONIC (Treatment of Nonalcoholic Liver Disease in Children) in which 173 children and adolescents with NAFLD were treated with Metformin (1 g/day) for 96 weeks did not find Metformin superior to placebo in attaining a sustained reduction in ALT levels or significant improvements in histological features [75].

In conclusion, although no drug is currently available as specific treatment for NAFLD, the available evidences clearly show a pivotal role of Metformin in improving metabolic alterations associated with NAFLD. Therefore, Metformin, because of its metabolic effects and its safety profile, remains a promising drug in NAFLD therapy, especially in patients that meet the diagnostic criteria of metabolic syndrome

Polycystic Ovary Syndrome (PCOs)

PCOs is the most common cause of menstrual dysfunction and hyperandrogenism in adolescents [76]. Sultan and Paris recommended that the adolescent girl meet four of the five following criteria: oligo- or amenorrhea >2 years after menarche, clinical hyperandrogenism, biochemical hyperandrogenism, insulin resistance or hyperinsulinemia, and polycystic ovaries on ultrasound [77]. Metabolic dysfunction constitutes an important risk associated with PCOs, and it can manifest at an early age. One-third of adolescents with PCOs meet criteria for the metabolic syndrome including (obesity, dyslipidemia, hypertension, and glucose intolerance) compared with approximately 5% of adolescents from the general population [78,79].

One study compared girls with an average age of 12 years who had PCOS to a group of obese, non-hyper-androgenic girls who were matched for age, percent body fat, and abdominal fat. Girls with PCOs were found to have an approximate 50% reduction in peripheral tissue insulin sensitivity compared with controls, and they also exhibited evidence of hepatic insulin resistance and compensatory hyper-insulinemia [80]. A cross-sectional community-based study showed that Obese girls with PCOS were more hirsute, hypertensive, and had significantly higher mean insulin and 2 h post 75 g glucose levels compared with non- obese PCOS [81]. Therefore, using Metformin for PCOS is attractive because this medication is known to improve these variables among adults with PCOS.

Metformin, through peripheral insulin-sensitizing effects, has been shown to exert several beneficial effects in trials of adult women with PCOs when used "off-label" to treat or prevent several clinical problems associated with PCOS including oligomenorrhea, hirsutism, infertility, obesity and glucose abnormalities [82].

A number of studies have demonstrated its efficacy in adolescents with PCOs, but they were short-term studies of 3-6 months in duration and had a limited number of participants [83,84]. One study has compared pre- and post-intervention outcomes of Metformin among 15 adolescents with PCOs. Following 3 months of treatment, glucose tolerance testing and free testosterone levels improved. Metformin

suppressed levels of androstenedione and 17-hydroxyprogesterone after an ACTH stimulation test, and authors called for randomized, placebo-controlled trials of Metformin for adolescents with PCOS to confirm their findings [85].

Endocrine society experts recommended that lifestyle management be considered first-line therapy for women with PCOS at increased metabolic risk. They suggest the use of Metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification and for women with PCOS with menstrual irregularity who cannot take or do not tolerate hormonal contraceptives (HCs). In addition it can be used as an adjuvant therapy for infertility to prevent ovarian hyper stimulation syndrome (OHSS) in women with PCOS undergoing in vitro fertilization. They disagree with the use of Metformin for management of hirsutism or acne [86].

Currently, Metformin appears to offer some benefit to adolescents with PCOs, but greater evidence of benefit is required to encourage its wide use by family physicians even if the goals of treatment may evolve with the patient's age.

Premature pubarche

Data indicate that girls with premature pubarche may not have a benign outcome and it may be associated with the metabolic syndrome and this may precede the development of clinical ovarian androgen excess in adolescence [87]. Ibanez et al, showed that 45 percent of postpubertal girls diagnosed with premature pubarche during childhood have an increased incidence of functional ovarian hyperandrogenism, with hirsutism, menstrual disturbances and elevated androgen level [82]. Data suggest a link between the triad of hyperinsulinemia, premature pubarche, and ovarian hyper-androgenism. Hyperinsulinemia is directly related to the degree of androgen excess. The early recognition of girls at risk of developing hyperinsulinaemic androgen excess might enable prevention in childhood [88,89]. In adolescents with premature pubarche, intervention with Metformin, as an insulin sensitizing agent, either as mono-therapy or in combination with the anti-androgen flutamide at low doses, appeared to have some beneficial effects on abdominal adiposity, androgen levels and indices of insulin resistance [90].

Girls born with low birth weight (LBW) and precocious pubarche are more insulin resistant with evidence of increased cardiovascular risk and have an increased incidence of a polycystic ovarian phenotype in young adulthood. Early Meformin therapy for 5 years proved valuable in delaying menarche, augmenting height and reducing total, visceral, and hepatic adiposity and lowering circulating levels of androgens and leptin in these girls compared to late therapy [91,92].

The anti-cancer effect of metformin

Metformin activates AMPK, which directly and indirectly reduces mammalian target of rapamycin (mTOR) complex 1 levels, playing a key role in controlling cell growth, proliferation, and metabolism [93, 94]. Many epidemiological, observational and laboratory data suggest an anticancer effect of Metformin in hepatocellular carcinoma, cancer breast and colorectal cancer and others. While others did not find significant anti-cancer effect of using Metformin. Up till now there is no consistent epidemiological evidence in clinical DM trial to support that Metformin is better than other hypoglycemic agent in lowering the cancer incidence. Several early-stage clinical trials are currently under way to investigate metformin's impact on cancer incidence, including colorectal, prostate, endometrial, and breast cancer [95].

Conclusions

Adolescents during their pubertal growth spurt have higher insulin resistance compared to other periods in life. The use of Metformin in many diseases in which insulin resistance constitutes an essential part of the pathogenesis appears promising with variable rates of success. These include obesity, prediabetes, polycystic ovary disease, premature pubarche, and non-alcoholic fatty liver disease. Metformin is a good insulin sensitizer that proved effective in adults and recently in adolescents with T2DM. However, long term controlled studies are still required to assess the degree and duration of effectiveness and safety of using Metformin in these diseases.

References

1. American Diabetes Association (2009) Standards of medical care in diabetes--2009. Diabetes Care 32 Suppl 1: S13-61.

2. Patade GR, Marita AR (2014) Metformin: A Journey from countryside to the bedside. J ObesMetab Res 1: 127-130.

3. CHEN KK, ANDERSON RC (1947) The toxicity and general pharmacology of N1-p-chlorophenyl-N5-isopropyl biguanide. J Pharmacol Exp Ther 91: 157-160.

4. Sterne J (1957) Du nouveau dans les antidiabetiques.La NN dimethylamineguanylguanide (N.N.D.G.) (The newantidiabetic NNdimethylamineguanylguanide). Maroc Med 36: 1295-1296.

5. Leone A, Di Gennaro E, Bruzzese F, Avallone A, Budillon A (2014) New perspective for an old antidiabetic drug: metformin as anticancer agent. Cancer Treat Res 159: 355-376.

6. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, et al. (2012) Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 122: 253-270.

7. Zhou G, Myers R, Li Y, Chen Y, Shen X, et al. (2001) Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108: 1167-1174.

8. Viollet B, Guigas B, Leclerc J, Hébrard S, Lantier L, et al. (2009) AMP-activated protein kinase in the regulation of hepatic energy metabolism: from physiology to therapeutic perspectives. Acta Physiol (Oxf) 196: 81-98.

9. Bogachus LD, Turcotte LP (2010) Genetic downregulation of AMPK-alpha isoforms uncovers the mechanism by which metformin decreases FA uptake and oxidation in skeletal muscle cells. Am J Physiol Cell Physiol 299: C1549-1561.

10. Yamaguchi S, Katahira H, Ozawa S, Nakamichi Y, Tanaka T, et al. (2005) Activators of AMP-activated protein kinase enhance GLUT4 translocation and its glucose transport activity in 3T3-L1 adipocytes. Am J Physiol Endocrinol Metab 289: E643-649.

11. Stephenne X, Foretz M, Taleux N, van der Zon GC, Sokal E, et al. (2011) Metformin activates AMP-activated protein kinase in primary human hepatocytes by decreasing cellular energy status. Diabetologia 54: 3101-3110.

12. Owen MR, Doran E, Halestrap AP (2000) Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 348 Pt 3: 607-614.

13. Saeedi R, Parsons HL, Wambolt RB, Paulson K, Sharma V, et al. (2008) Metabolic actions of metformin in the heart can occur by AMPK-independent mechanisms. Am J Physiol Heart Circ Physiol 294: H2497-2506.

14. Collier CA, Bruce CR, Smith AC, Lopaschuk G, Dyck DJ (2006) Metformin counters the insulin-induced suppression of fatty acid oxidation and stimulation of triacylglycerol storage in rodent skeletal muscle. Am J Physiol Endocrinol Metab 291: E182-189.

15. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, et al. (2013) Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 494: 256-260.

16. Burcelin R (2014) The antidiabetic gutsy role of metformin uncovered? Gut 63: 706-707.

17. Maida A, Lamont BJ, Cao X, Drucker DJ (2011) Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-α± in mice. Diabetologia 54: 339-349.

18. Cho YM, Kieffer TJ (2011) New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser. Diabetologia 54: 219-222.

19. Boyle JG, McKay GA, Fisher M (2010) Drugs for Diabetes: Part 1 Metformin. Br J Cardiol 17: 231-234.

20. [No authors listed] (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352: 854-865.

21. Bristol-Myers Squibb (2008) U.S. Food and Drug Administration. Glucophage (metformin hydrochloride tablets) Label Information; August 27, 2008.

22. Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE (2012) Metformin pathways: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics 22: 820-827.

23. http://www.drugs.com/pro/metformin.html

24. Salpeter S, Greyber E, Pasternak G, Salpeter E (2006) Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev: CD002967.

25. https://pharmacy.unc.edu/research/labs/thakker-laboratory/poster-presentations/han

26. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32: 193-203.

27. http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf

28. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di19-diabetes-blood-glucose-control.pdf

29. Rojas LB, Gomes MB (2013) Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr 5: 6.

30. de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, et al. (2010) Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ 340: c2181.

31. Gungor N, Hannon T, Libman I, Bacha F, Arslanian S (2005) Type 2 diabetes mellitus in youth: the complete picture to date. Pediatr Clin North Am 52: 1579-1609.

32. Kaufman FR (2002) Type 2 Diabetes in Children and Young Adults: A "New Epidemic. Clinical Diabetes October 20: 217-218.

33. Copeland KC, Silverstein J, Moore KR, Prazar GE, Raymer T, et al. (2013) American Academy of Pediatrics. Management of newly diagnosed type 2 Diabetes Mellitus (T2DM) in children and adolescents. Pediatrics 131: 364-382.

34. Quinn SM, Baur LA, Garnett SP, Cowell CT (2010) Treatment of clinical insulin resistance in children: a systematic review. Obes Rev 11: 722-730.

35. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ (2009) Type 2 diabetes in children and adolescents. Pediatr Diabetes 10 Suppl 12: 17-32.

36. TODAY Study Group, Zeitler P, Hirst K, Pyle L, Linder B, et al. (2012) A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 366: 2247-2256.

37. McGovern L, Johnson JN, Paulo R, Hettinger A, Singhal V, et al. (2008) Clinical review: treatment of pediatric obesity: a systematic review and meta-analysis of randomized trials. J Clin Endocrinol Metab 93: 4600-4605.

38. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, et al. (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346: 393-403.

39. Glueck CJ, Fontaine RN, Wang P, Subbiah MT, Weber K, et al. (2001) Metformin reduces weight, centripetal obesity, insulin, leptin, and low-density lipoprotein cholesterol in nondiabetic, morbidly obese subjects with body mass index greater than 30. Metabolism 50: 856-861.

40. Pernicova I, Korbonits M (2014) Metformin--mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol 10: 143-156.

41. Iughetti L, China M, Berri R, Predieri B (2011) Pharmacological treatment of obesity in children and adolescents: present and future. J Obes 2011: 928165.

42. Brufani C, Crinò A, Fintini D, Patera PI, Cappa M, et al. (2013) Systematic review of metformin use in obese nondiabetic children and adolescents. Horm Res Paediatr 80: 78-85.

43. Srinivasan S, Ambler GR, Baur LA, Garnett SP, Tepsa M, et al. (2006) Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. J Clin Endocrinol Metab 91: 2074-2080.

44. Ou HY, Cheng JT, Yu EH, Wu TJ (2006) Metformin increases insulin sensitivity and plasma beta-endorphin in human subjects. Horm Metab Res 38: 106-111.

45. Park MH, Kinra S, Ward KJ, White B, Viner RM (2009) Metformin for obesity in children and adolescents: a systematic review. Diabetes Care 32: 1743-1745.

46. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, et al. (2011) Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes 60: 477-485.

47. Atabek ME, Pirgon O (2008) Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. J Pediatr Endocrinol Metab 21: 339-348.

48. Wiegand S, l'Allemand D, Hubel H, Krude H, Burmann M, et al. (2010) Metformin and placebo therapy both improve weight management and fasting insulin inobese insulin resistant adolescents: a prospective, placebo-controlled, randomized study. Eur J Endocrinol 163: 585-592.

49. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, et al. (2011) Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. Diabetes 60: 477-485.

50. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, et al. (2011) American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 17 Suppl 2: 1-53.

51. Goran MI, Gower BA (2001) Longitudinal study on pubertal insulin resistance. Diabetes 50: 2444-2450.

52. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, et al. (1999) Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 48: 2039-2044.

53. Mortensen HB, Hougaard P (1997) Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 countries. The Hvidøre Study Group on Childhood Diabetes. Diabetes Care 20: 714-720.

54. DCCT Research Group (1994) Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 125: 177-188.

55. Hamilton J, Cummings E, Zdravkovic V, Finegood D, Daneman D (2003) Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. Diabetes Care 26: 138-143.

56. Brufani C, Fintini D, Nobili V, Patera PI, Cappa M, et al. (2011) Use of metformin in pediatric age. Pediatr Diabetes 12: 580-588.

57. Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, et al. (2010) The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia 53: 809-820.

58. Abdelghaffar S, Attia AM (2009) Metformin added to insulin therapy for type 1 diabetes mellitus in adolescents. Cochrane Database Syst Rev: CD006691.

59. Nadeau KJ, Chow K, Alam S, Lindquist K, Campbell S, et al. (2014) Effects of low dose metformin in adolescents with type I diabetes mellitus: a randomized, double-blinded placebo-controlled study. Pediatr Diabetes.

60. Meyer L, Guerci B (2003) Metformin and insulin in type 1 diabetes: the first step. Diabetes Care 26: 1655-1656.

61. Farrell GC, Larter CZ (2006) Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 43: S99-99S112.

62. Wieckowska A, McCullough AJ, Feldstein AE (2007) Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. Hepatology 46: 582-589.

63. Mathur P, Das MK, Arora NK (2007) Non-alcoholic fatty liver disease and childhood obesity. Indian J Pediatr 74: 401-407.

64. Huang MA, Greenson JK, Chao C, Anderson L, Peterman D, et al. (2005) One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. Am J Gastroenterol 100: 1072-1081.

65. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE (2005) A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther 21: 871-879.

66. Nobili V, Manco M, Ciampalini P, Alisi A, Devito R, et al. (2008) Metformin use in children with nonalcoholic fatty liver disease: an open-label, 24-month, observational pilot study. Clin Ther 30: 1168-1176.

67. Nadeau KJ, Ehlers LB, Zeitler PS, Love-Osborne K (2009) Treatment of non-alcoholic fatty liver disease with metformin versus lifestyle intervention in insulin-resistant adolescents. Pediatr Diabetes. 10: 5-13.

68. Loomba R, Lutchman G, Kleiner DE, Ricks M, Feld JJ, et al. (2009) Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. Aliment Pharmacol Ther 29: 172-182.

69. Nair S, Diehl AM, Wiseman M, Farr GH Jr, Perrillo RP (2004) Metformin in the treatment of non-alcoholic steatohepatitis: a pilot open label trial. Aliment Pharmacol Ther 20: 23-28.

70. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, et al. (2005) A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 100: 1082-1090.

71. De Oliveira MS, Stefano JT, De Siqueira ERF (2008) "Combination of N-acetylcysteine and metformin improves histological steatosis and fibrosis in patients with non-alcoholic steatohepatitis," Hepatol Res 38: 159-165.

72. Idilman R, Mizrak D, Corapcioglu D (2008) "Clinical trial: insulin-sensitizing agents may reduce consequences of insulin resistance in individuals with non-alcoholic steatohepatitis," Aliment Pharmacol Ther 28: 200-208.

73. Janiec DJ, Jacobson ER, Freeth A, Spaulding L, Blaszyk H (2005) Histologic variation of grade and stage of non-alcoholic fatty liver disease in liver biopsies. Obes Surg 15: 497-501.

74. Mazza A, Fruci B, Garinis GA, Giuliano S, Malaguarnera R, (2012) The Role of Metformin in the Management of NAFLD. Experimental Diabetes Research 12: 155-168.

75. Alkhouri N, Feldstein AE (2012) The TONIC trial: a step forward in treating pediatric nonalcoholic fatty liver disease. Hepatology 55: 1292-1295.

76. Blank SK, Helm KD, McCartney CR, Marshall JC (2008) Polycystic ovary syndrome in adolescence. Ann N Y Acad Sci 1135: 76-84.

77. Sultan C, Paris F (2006) Clinical expression of polycystic ovary syndrome in adolescent girls. Fertil Steril 86 Suppl 1: S6.

78. Coviello AD, Legro RS, Dunaif A (2006) Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J Clin Endocrinol Metab 91: 492-497.

79. Alemzadeh R, Kichler J, Calhoun M (2010) Spectrum of metabolic dysfunction in relationship with hyperandrogenemia in obese adolescent girls with polycystic ovary syndrome. Eur J Endocrinol 162: 1093-1099.

80. Lewy VD, Danadian K, Witchel SF, Arslanian S (2001) Early metabolic abnormalities in adolescent girls with polycystic ovarian syndrome. J Pediatr 138: 38-44.

81. Joshi B, Mukherjee S, Patil A, Purandare A, Chauhan S, et al. (2014) A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. Indian J Endocrinol Metab 18: 317-324.

82. Nestler JE (2008) Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med 358: 47-54.

83. La Marca A, Artensio AC, Stabile G, Volpe A (2005) Metformin treatment of PCOS during adolescence and the reproductive period. Eur J Obstet Gynecol Reprod Biol 121: 3-7.

84. Ibáñez L, Valls C, Ferrer A, Marcos MV, Rodriguez-Hierro F, et al. (2001) Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab 86: 3595-3598.

85. Lewy V, Danadian K, Saad R (2002) Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 87: 1555-1559.

86. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, et al. (2013) Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 98: 4565-4592.

87. Ibanez L, Potau N, Virdis R, Zampolli M, Terzi C, et al. (1993) Postpubertal outcome in girls diagnosed of premature pubarche during childhood: increased frequency of functional ovarian hyperandrogenism. J Clin Endocrinol Metab 76: 1599-1603.

88. Palomba S, Orio F Jr, Falbo A, Manguso F, Russo T, et al. (2005) Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobeseanovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab 90: 4068-4074.

89. Idkowiak J, Lavery GG, Dhir V, Barrett TG, Stewart PM, et al. (2011) Premature adrenarche: novel lessons from early onset androgen excess. Eur J Endocrinol 165: 189-207.

90. Williams RM, Ward CE, Hughes IA (2012) Premature adrenarche. Arch Dis Child 97: 250-254.

91. Ibáñez L, Lopez-Bermejo A, Diaz M, Marcos MV, de Zegher F (2011) Early metformin therapy to delay menarche and augment height in girls with precocious pubarche. Fertil Steril 95: 727-730.

92. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F (2011) Early metformin therapy (age 8-12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. J Clin Endocrinol Metab 96: E1262-1267.

93. Jalving M, Gietema JA, Lefrandt JD, de Jong S, Reyners AK, et al. (2010) Metformin: taking away the candy for cancer? Eur J Cancer 46: 2369-2380.

94. Pierotti MA, Berrino F, Gariboldi M, Melani C, Mogavero A, et al. (2013) Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects. Oncogene 32: 1475-1487.

95. Meng S (2014) The Anticancer Effect of Metformin, the Most Commonly Used Anti-Diabetes Drug. J Endocrinol Diabetes Obes 2: 1030.