SYSTEMATIC REVIEW ARTICLE PHARMACOLOGIA

DOI: 10.5567/pharmacologia.2013.511.518

Metformin Treatment for Obesity in Children and Adolescents: A Meta-analysis and Review of Literature

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ABSTRACT

Background: Obesity in children is becoming a global health problem. Metformin use to treat obesity in children is increasingly attracting the attention of clinicians, however, for evidence-based practice, it is important to systematically analyze the effectiveness of metformin for childhood/adolescence obesity in clinical trials. **Method:** Literature search was made in multiple electronic databases. Methods of analyses comprised meta-analysis (fixed effects model as well as random effect model) for the determination of statistical significance between metformin treatment and several variables of study outcomes and meta-regression analysis for the impact of these variables on metformin treatment. **Results:** Eight studies were included in the meta-analysis. Study intervention duration ranged from 12 to 52 weeks while population size ranged from 28 to 348 participants. Moreover, Participant's age ranged from 6 to 19 years of age. This meta-analysis reveals significant effect of metformin treatment in reducing BMI with effect size ranged in magnitude from -3.17 kg m^{-2} (24) to -0.16 kg m^{-2} (26). The fixed effects pooled results demonstrated a drop in BMI of 1.08 kg m^{-2} with a 95% confidence interval of -1.14 and -0.03 kg m^{-2} ($p<0.01$). The random effects model demonstrated a larger effect size with a value of -1.46 kg m^{-2} and confidence interval of -1.91 to -1.01 kg m^{-2} ($p<0.01$). Metformin tolerability was consistent in all studies. **Conclusion:** It is demonstrated that metformin is efficacious with minor side effects, however, larger trials are required to reach at conclusive evidence.

Key words: Metformin, childhood, adolescent, obesity, body mass index, weight

Pharmacologia 4 (8): 511-518, 2013

INTRODUCTION

Childhood obesity has become a major health problem worldwide (Morrison *et al*., 2008; Steinberger *et al*., 2009). Adverse health issues associated with the consequences of childhood obesity are observed in populations in all continents. These include type 2 Diabetes Mellitus and cardiovascular disease (Dixon, 2010). In addition, there is an increased incidence of elevated blood pressure, insulin resistance and dyslipidemia, all of these are the components constitute metabolic syndrome. Studies show that metabolic syndrome is an independent risk factor for the development of cardiovascular disease (Huang *et al*., 2009; Schubert *et al*., 2009).

Behavioral modification and lifestyle changes represent current approaches utilized to ameliorate the obesity and associated co-morbidities. Strategies focusing on low-caloric diets high in fruits and vegetables along with exercise have great potential to reduce fat mass but unfortunately these efforts have demonstrated limited efficacy (Savoye *et al*., 2007; Wilfley *et al*., 2007; McGovern *et al*., 2008; Kalarchian *et al*., 2009). This has led to a keen interest in the development of newer and more effective approaches. In this regard, chemotherapeutic regimens have always remained a priority in research. Metformin has received a good deal of attention due to its potential therapeutic role in pediatric obesity management (August *et al*., 2008).

Metformin suppresses hepatic glucose production at high concentrations (DeFronzo *et al*., 1991), improves peripheral insulin sensitivity (Cigolini *et al*., 1984) and reduces weight gain in adults with type 2 Diabetes Mellitus (UKPDS Group, 1998; Golay, 2008). Metformin has also demonstrated weight stabilization or a mild weight reduction characteristics in adults with (DeFronzo and Goodman, 1995; Stumvoll *et al*., 1995; Lee and Morley, 1998; DPPRG, 2012) and without diabetes (Munro *et al*., 1969; Fontbonne *et al*., 1996). A number of Randomized Controlled Trials (RCTs) have been carried out in obese, non-diabetic, insulin-resistant pediatric and adolescent populations (Lutjens and Smith, 1977; Freemark and Bursey, 2001; Srinivasan *et al*., 2006; Fu *et al*., 2007; Atabek and Pirgon, 2008; Love-Osborne *et al*., 2008; Wilson *et al*., 2010; Rezvanian *et al*., 2010; Yanovski *et al*., 2011). However, the variability of outcomes in these studies necessitates to

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conduct a meta-analysis of these results in order to improve the state of the evidence. The present systematic review and meta-analysis of pooled data from these randomized controlled trials has been conducted in order to examine the evidence of metformin efficacy in childhood/adolescence obesity. In addition, meta-regression analysis has also been carried out to explore independent predictors of metformin efficacy.

MATERIALS AND METHODS

Literature search and study selection: A systematic literature search for relevant double-blind studies published during 2001 and 2012 was conducted in PUBMED and EMBASE digital databases. Eleven search terms relating to overweight, obesity, diabetes and metformin were used to retrieve articles reporting RCTs evaluating the efficacy of metformin in obese children/adolescents (age = 19 years). Additional articles were manually searched by from the reference lists of identified papers. The search was restricted to articles published in English language. Studies that included diabetics or those with secondary causes of obesity were excluded from this analysis. Moreover, of the selected studies, only randomized phase trials of metformin treatment have been taken into consideration for this meta-analysis. Primary outcomes of interest were BMI (weight in kilograms divided by the height in squared meters; kg m^{-2}), homeostasis model of assessment-insulin resistance (HOMA-IR; glucose X insulin/22.5) and fasting insulin levels. Secondary outcomes consisted of total triglyceride levels, total cholesterol levels, LDL-cholesterol levels, HDL-cholesterol and blood pressure, systolic as well as diastolic.

Statistical analysis: The analysis was conducted using STATA Version 9.1 (College Station, Texas) and Tableau (Seattle, Washington) software. Methods of analyses comprised meta-analysis (fixed effects model as well as random effect model) for the determination of statistical significance between metformin treatment and several variables of study outcomes and meta-regression analysis for the determination of impact of several independent variables on metformin treatment. Briefly, to calculate effect size, differences in means and standard errors were calculated for each study. Weights for each study were calculated as inverse variance. The synthesized data were subjected to the homogeneity test (random I–V heterogeneity methods). The outcomes were compared by using Cohen, Hedges and the Glass statistics. For meta-regression analysis, random effect model was used. Between-study variance and coefficients were estimated by weighted least squares. This software uses residual (restricted) maximum likelihood (ReML) as a default algorithm component and is also powered by moment's technique. Post-estimation tools utilized to strengthen the results also included empirical Bayes (EmBayes) estimates.

RESULTS

The literature search finally led to the identification of nine studies, eight of which met the criteria for inclusion in this meta-analysis (Table 1). Results of these studies were published between 2001 and 2011. Five of the eight studies were conducted in the United States (Freemark and Bursey, 2001; Srinivasan *et al*., 2006; Love-Osborne *et al*., 2008; Wilson *et al*., 2010; Yanovski *et al*., 2011), one in China (Fu *et al*., 2007), one in Iran, (Rezvanian *et al*., 2010) and one in Turkey (Atabek and Pirgon, 2008). Six of these trials utilized a treatment design that was complemented with behavioral modifications and lifestyle changes. Study intervention duration ranged from 12-52 weeks. Study population size ranged from 28 to 348 participants. Participants ranged in age from 6 to 19 years. Six of the studies stratified patients by gender. The highest proportion of female participants was 72% (Love-Osborne *et al*., 2008) and the lowest 40% (Fu *et al*., 2007). Four studies stratified patients by their ethnic backgrounds. The highest proportion of minority participants was 90% (Love-Osborne *et al*., 2008) while the lowest 45% (Freemark and Bursey, 2001). Minority participants were defined as those with the following racial backgrounds: Hispanic, African-American, Native American, Asian, Pacific Islander and Indian Subcontinent.

Almost all of the studies revealed a good deal of tolerability of metformin treatment as the side effects were lesser as well as well-manageable. A synthesis of the prevalence of most important side effects reported in all these studies has been presented in Table 2.

Meta-analysis

Effects of metformin treatment on BMI, HOMA-IR and fasting insulin levels: Overall, both the models of the meta-analysis comprising of eight RCTs of 12-52 weeks duration identified a significant effect of metformin treatment in reducing BMI with effect size ranged in magnitude from -3.17 kg m^{-2} (Fu *et al*., 2007) to -0.16 kg m^{-2} (Love-Osborne *et al*., 2008). The fixed effects pooled results demonstrated a drop in BMI of 1.08 kg m^{-2} with a 95% confidence interval of -1.14 and -0.03 kg m^{-2} ($p<0.01$). The Random effect model demonstrated a larger effect size with a value of -1.46 kg m^{-2} and confidence interval of -1.91 to -1.01 kg m^{-2} ($p<0.01$). Only one study (Love-Osborne *et al*., 2008) failed to demonstrate a statistically significant association) between the metformin treatment and BMI reduction (Table 3).

Table 1: Study-wise patient populations, dosage regimen, co-interventions and other characteristics of the included studies

Population									
	Metformin		Placebo						
N	Start	End	Start	End	Dosage (mg/day)/ duration	Co-interventions	Remarks	Limitations	References
32	15	14	17	15	1,000/6 months	None	No dietary restrictions were advised	Small population size with multi-ethnic and both-sexes participants	Freemark and Bursey (2001)
34	13	12	15	14	Up to 1,000/6 months	None	Crossover study; metformin group received placebo later (n=12/15) and placebo group received metformin later (n=10/13)	Small population size with both sexes included	Srinivasan *et al.* (2006)
348	36	20	24	-	500/3 months	Lifestyle modification (dietary restriction with low intensity exercise advice)	Results for metabolic MS group are reported only. Pre-exclusion sample size is reported (participants who refused/did not meet inclusion criteria inclusive)	Short duration study	Fu *et al.* (2007)
120	90	90	30	30	1,000/6 months	Lifestyle modification (diet restriction, exercise and behavioral therapy)			Atabek and Pirgon (2008)
85	60	48	25	16	500-1,700/6 months	Lifestyle modification (dietary restrictions and exercise advice)	Participants on metformin who adapted reduced portion size strategy significantly reduced their BMI (-1.3 kg m^{-2})	Small population size in terms of inclusion of multiethnic participants	Love-Osborne *et al.* (2008)
68	39	27	38	27	500-2,000/52 weeks	Lifestyle modification (Weigh of life LITE program; 10 sessions)	Fluctuation in BMI in the placebo group remained unexplained		ERFC (2010)
180	45	41	45	42	500-1,500/12 weeks	Lifestyle modification (increase in exercise and improvement in eating behavior advice)	In this triple-masked RCT, groups studied were: metformin (n=45), fluoxetine (n=45), metformin+ fluoxetine (n=45), and placebo (n=45). Only metformin group data are included in meta-analysis.	Shorter study period	Rezvanian *et al.* (2010)
100	53	45	47	40	250-1,000/6 months	Lifestyle modification (low energy diet and physical activity)		Study is delimited to severely obese adolescents	Yanovski *et al.* (2011)

In a fixed effects model, the analysis showed a decrease of 1.06 (p<0.002) HOMA-IR while the random effects model did not reveal any statistically significant relation between metformin treatment and HOMA-IR though it resulted in an effect size of -2.57 (p = 0.07)(Table 4). As far as the effect of metformin on fasting insulin levels is concerned, the meta-analysis revealed fixed effect value of -4.47 (p<0.002) and random effects value of -7.13 (p<0.005) (Table 4).

Table 2: Common side effects noted during various studies after metformin therapy and their overall magnitude

	Prevalence: Metformin vs. placebo	
Side effect	Study-wise	Overall
Vomiting	15 vs. 3% (27), 41.5 vs. 21.3% (29)	9 vs. 4%
Nausea	23 vs. 8% (27); 6.7% vs. (29); 7% vs. (22)	4 vs. 1%
Diarrhea	50 vs. (22); 2.2% vs. (25)	3 vs. 0%
Loose motions	41.5 vs. 17% (29); 7.3 vs. 0% (28)	4 vs. 1%
Abdominal pain/ discomfort	50 vs. 0% (22); 5 vs. 0% (28)	3 vs. 0%
Gastrointestinal problems	29 vs. 19% (26)	6 vs. 3%
Increased bowl movement	6.7 vs. 0% (24)	1 vs. 0%
Respiratory tract infections	46 vs. 23% (27)	6 vs. 3%
Reduced appetite	23.3 vs. 0%(24)	2 vs. 0%
Musculoskeletal problems	13 vs. 18% (27)	2 vs. 1%
Fatigue	37.7 vs. 14.9% (29)	7 vs. 3%
Headache	31 vs. 21% (27); 5 vs. 0% (28)	5 vs. 0%

Table 3: Effect size of metformin treatment on BMI in different included studies and meta-analysis

Study	Effect size	95% CI	Weight	p
Freemark and Bursey (2001)	-0.73	-0.86, -0.60	17.66	<0.001
Srinivasan *et al.* (2006)	-1.26	-2.02, -0.51	0.54	0.001
Fu *et al.* (2007)	-3.17	-3.63, -2.71	1.46	<0.001
Atabek and Pirgon (2008)	-2.73	-3.22, -2.24	1.29	<0.001
Love-Osborne *et al.* (2008)	-0.16	-0.97, 0.65	0.48	0.701
ERFC (2010)	-1.10	-2.08, -0.12	0.32	0.027
Rezvanian *et al.* (2010)	-1.10	-1.16, -1.04	77.73	<0.001
Yanovski *et al.* (2011)	-1.09	-1.87, -0.31	0.51	0.006
Fixed effects pooled ES	-1.08	-1.14, -1.03	100.00	<0.001
Random Effects Pool ES	-1.46	-1.91, -1.01	100.00	<0.001

CI: Confidence interval

Effect of metformin on cholesterol, triglycerides and blood pressure: Not all studies mentioned data regarding the effect of metformin on lipid profile; cholesterol (4 studies), HDL/LDL (4 studies) and two studies reported pre- and post-treatment blood pressure data. The effect of metformin treatment was found to be significant in reducing total cholesterol levels (ES -0.87; CI -12.53 to 3.46; P<0.003) and increasing HDL cholesterol levels (ES 1.5; CI 0.28 to 2.71; p = 0.02). However, no statistically significant correlation was observed in the meta-analysis of the metformin treatment effect on triglycerides (ES -0.38; CI -1.11 to 0.35; p = 0.31), LDL cholesterol (ES -0.79; CI -4.14 to 2.57; p = 0.65), systolic blood pressure (ES -0.19; CI -1.09 to 0.72; p = 0.69) and diastolic blood pressure (ES 0.32; CI -0.32 to 0.76; p = 0.42).

Meta-regression: Meta-regression analysis was carried out in order to explore independent variables that might have exerted impacts on the efficacy of metformin treatment in selected eight RCTs. Of the nine variable (weight, mean age, initial BMI, sample size, percentage of females, attrition rate, behavioral interventions, length of study, percent minority participants), at 95% confidence level, only sample size (coefficient = -0.01; t = -2.53; p = 0.05) and female gender (coefficient = 10.68; t = 6.23; p<0.001) were recognized as independent variables to regress metformin efficacy. Other variables that had no effect on the magnitude of the metformin induced change in BMI included initial weight (p = 0.11), initial BMI (p = 0.12), mean age (p = 0.18), racial composition of the total sample (p = 0.51), study attrition rate (p = 0.47), behavioral intervention (p = 0.40) and study length (p = 0.46). Meta-regression analysis also failed to demonstrate any statistically significant association between higher metformin dosage and attrition rate (p = 0.34; Fig. 1a), higher metformin dosage and gastrointestinal side effect incidence trend (p = 0.75; Fig. 1b) and attrition rate of the participants because of the side effects prevalence (p = 0.82; Fig. 1c).

Table 4: Effects of metformin treatment on HOMA-IR and fasting insulin levels in different included studies and the meta-analysis

	HOMA-IR				Fasting insulin levels			
Study	ES	95% CI	Weight	p	ES	95% CI	Weight	p
ERFC (2010)	0.70	-1.26, 2.66	11.48	0.48	NA	NA	NA	NA
Srinivasan *et al.* (2006)	0.17	-0.82, 1.16	44.83	0.74	-2.20	-3.90, -0.50	68.05	0.01
Yanovski *et al.* (2011)	-1.54	-4.70, 1.62	4.42	0.34	NA	NA	NA	NA
Fu *et al.* (2007)	-2.74	-5.70, 0.22	5.03	0.07	-5.75	-10.45, -1.06	8.88	0.02
Atabek and Pirgon (2008)	-2.69	-3.83, -1.55	34.08	<0.001	-10.60	-14.73, -6.47	11.45	<0.001
Freemark and Bursey (2001)	-54.10	-70.34, -37.86	0.17	<0.001	-10.70	-14.80, -6.60	11.62	<0.001
Fixed effects outcome	-1.06	-1.72, -0.39	100.00	<0.002	-4.47	-5.86, -3.07	100.00	<0.002
Random effects outcome	-2.57	-5.38, 0.24	100.00	0.07	-7.13	-12.07, -2.18	100.00	<0.005

CI: Confidence interval ES: Effect size and NA: Not attempted

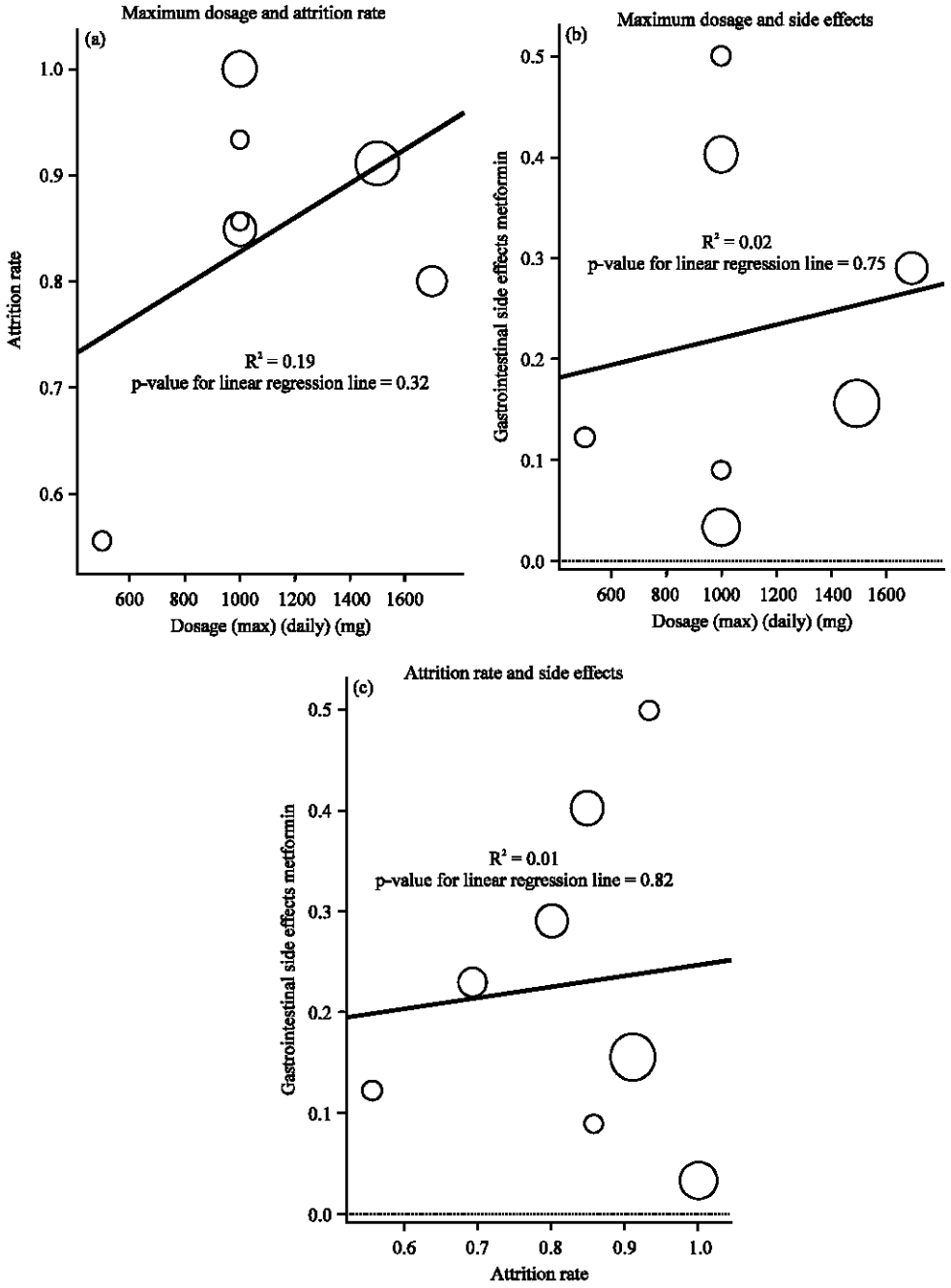

Fig. 1(a-c): (a) Meta-regression analysis for the association between maximum metformin dosage and attrition rate, (b) Maximum metformin dosage and side effects and (c) Attrition rate and side effects. Effect of metformin on BMI is represented by circle color and population size by circle size

DISCUSSION

Obesity is no more rarely associated with the development of metabolic syndrome, a problem that predisposes individuals to the development of cardiovascular disease in later years (Huang *et al*., 2009; Schubert *et al*., 2009). Moreover, the risk of the development of Type 2 diabetes in an overweight individual is directly proportional to the severity of the obese state (Zimmet *et al*., 1992; Srinivasan *et al*., 1999). Treatment of childhood obesity along with its associated

comorbid illnesses is therefore of paramount importance. In this regard, the present systematic review and meta-analysis of the published RCTs serve to shed light on metformin treatment as a potential therapeutic intervention in this hyperinsulinemic, obese patient population.

Meta-analysis using both pooled fixed and random effects models demonstrated that metformin therapy produced a statistically significant decline in BMI in the treated participants of study population. The fixed effects results demonstrated that metformin treatment was associated with BMI decline of 1.08 kg m^{-2} with a 95% confidence interval of -1.14 to -1.03 kg m^{-2} ($p<0.01$). The random effects model revealed a larger effect; -1.46 kg m^{-2} BMI decline with confidence interval of -1.91 kg m^{-2} to -1.01 kg m^{-2} ($p<0.01$). Previously, in a meta-analysis conducted by Park *et al*. (2009) a significant metformin therapeutic effect (1.42 kg m^{-2}) has been reported which is similar in magnitude to that of achieved in our study.

Dietary modifications, lifestyle changes and exercise comprise an integral component of the overall long term management of obesity and metabolic syndrome. The findings of this review serve to reiterate that metformin may substantiate other strategic interventions such as behavioral modifications and dietary changes. Though meta-regression analysis fails to provide any significant association between metformin induced change in BMI seen herein with behavioral interventions ($p = 0.86$), yet several lines of evidence suggest that there could be multi-mechanisms of metformin mode of action. Love-Osborne *et al*. (2008) have reported non-significant effect of metformin on BMI overall but they found a significant effect in individuals who observed lifestyle changes such as those who reduced portion size. In the study of Fu *et al*. (2007), 23.3% participants under metformin treatment reported reduced appetite. There is some evidence that metformin may also act to reduce food intake in obese subjects (Paolisso *et al*., 1998).

A meta-analysis of 64 RCTs performed by Oude Luttikhuis *et al*. (2009) encompassing over five thousand participants showed that medication alone may not be as effective as behavioral interventions in reducing BMI. They noted effects sizes of Orlistat and sibutramine as -0.76 kg m^{-2} (-1.07 to -0.44) and -1.66 kg m^{-2} (-1.89 to -1.43), respectively following 6 months treatments. McGovern *et al*. (2008) examined the data from three studies and failed to find any notable metformin effect after 6 months of treatment; -0.17 kg m^{-2} (95% CI -0.62 to -0.28). Sukkari *et al*. (2010) have also reported a greater benefit for lifestyle intervention when compared with metformin treatment. Behavioral interventions have shown effect up to -3.04 kg m^{-2} (95% CI -3.14 to -2.94) at 6 months and at 12 months of follow-up.

In this meta-analysis, the HOMA-IR data taken from four studies (Srinivasan *et al*., 2006; Fu *et al*., 2007; ERFC, 2010; Yanovski *et al*., 2011) revealed no statistically significant metformin effect while two (Freemark and Bursey, 2001; Atabek and Pirgon, 2008) reported a strong metformin effect. Though, in a fixed effects model, based on these six studies, a statistically significant metformin effect has been noted, the random effects model did not reveal significant effect. Keeping in view a great deal of disparity in participant characteristics, it is reasonable to give more credence to the random effects result (Riley *et al*., 2011).

All four studies (Freemark and Bursey, 2001; Srinivasan *et al*., 2006; Fu *et al*., 2007; Atabek and Pirgon, 2008) that reported baseline and end of metformin treatment fasting insulin levels yielded a statistically significant association. In aggregate, a strong metformin effect on this parameter has been noticed. In addition, a metformin induced significant effect was also seen in total cholesterol ($p<0.003$) and HDL cholesterol ($p = 0.02$) levels.

The meta-regression outcomes indicated that the percentage of female participants was directly associated with increased metformin efficacy ($p = 0.003$). This observation owes its major weight from the study of Love-Osborne *et al*. (2008) who found that females were twice as likely as males to decrease their BMI by 5% and were less likely to gain weight as compared to males. This gender-biased metformin effect has also been reported in another study (Freemark and Bursey, 2001). The reason for these differences is not as clear. This may be attributed to the effects on leptin levels in metformin treated girls as is observed by Fu *et al*. (2007). It is well-established that leptin levels in the young adolescents remain higher in females as compared to males (Carlsson *et al*., 1997; Kiess *et al*., 1998).

The incidence of serious side effects was found to be extremely rare. Minor gastrointestinal side effects were common in study patients and present a statistically significantly greater number taking metformin when compared with those taking placebo. The higher prevalence rates of side effects are generally implicated for higher attrition rates in many clinical trials. In the present study, however, meta-regression analysis did not reveal a significant association between the incidence of gastrointestinal side effects and attrition rate. There was also no significant correlation between the dosage of metformin and the frequency of gastrointestinal side effects as well.

CONCLUSION

The present study revealed that sample size served as an independent variable in the assessment of metformin efficacy. The relatively small number of patients in the pooled analysis may have served to

obscure the true potency of this medication. In addition, there may not have been sufficient statistical power to detect other relevant treatment effects. Nonetheless, these results are encouraging; metformin demonstrated significant efficacy with only minor associated side effects. In future, larger studies are recommended to evaluate the significance; not only on metformin but also on second generation sulfonylureas such as glipizide, to definitively determine their role in the treatment of obesity in this patient population.

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