Araştırma Makalesi
Research Article

Efficacy of metformin therapy in obese children with insulin resistance

İNSÜLİN DİRENCİ OLAN OBEZ ÇOCUKLARDA METFORMİN TEDAVİSİNİN ETKİNLİĞİ

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ABSTRACT

Objective: Obesity and insulin resistance is an important problem of general public health as well as pediatric endocrinology due to the disorders it causes. Metformin, a well-known oral antidiabetic, is increasingly being a common choice in treatment of obese and insulin resistant children. In this study, it was aimed to retrospectively evaluate the subjects who used metformin treatment due to insulin resistance and exogenous obesity in our clinic and to assess the effects of metformin on anthropometric and metabolic variables.

Materials and Methods: The medical records of the 36 patients, who were started metformin therapy due to obesity and insulin resistance and were followed-up in the Pediatric Endocrinology Department of Dokuz Eylül University Medical Faculty between 2005-2015, were retrospectively evaluated. The anthropometric and metabolic variables of these individuals at the sixth month of treatment were compared with basal values.

Results: Statistically significant decrease was detected after six months of metformin treatment in weight SDS (Standard Deviation Score) (mean 2.29 to 1.8), BMI (mean 31.3kg/m^2 to 29.8kg/m^2), and BMI SDS (mean 2.2 to 1.9) ($p<0.001$). A mean reduction of 2.41±1.93kg/m^2 was present in BMI values of study subjects ($p<0.001$). Statistically significant reductions were found in post-treatment fasting insulin, fasting glucose/insulin ratio, HOMA-IR and Quick index values ($p<0.05$).

Conclusion: Metformin is one of the treatment options in obese adolescents with insulin resistance. In our study, it was observed that improvement in anthropometric measurements and metabolic parameters was achieved without any serious side effects in patients who received metformin treatment.

Keywords: adolescent, insulin resistance, metformin, obesity

ÖZ

Amaç: Obezite ve insülin direnci, yol açtığı bozukluklar nedeniyle pediatrik endokrinolojinin yanı sıra genel toplum sağlığının önemli bir sorunudur. Bilinen eski bir oral antidiyabetik olan Metforminin obez ve insülin direnci olan çocuklarda kullanımı her geçen gün yaygınlaşmaktadır Bu çalışmada kliniğimizde obezite ve insülin direnci için metformin tedavisi alan olguların tedavi öncesi ve sonrası antropometrik ve metabolik parametreleri karşılaştırılarak tedavi etkinliğinin değerlendirilmesi amaçlanmıştır.

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Gereç ve Yöntem: Dokuz Eylül Üniversitesi Tıp Fakültesi Çocuk Endokrinoloji Bilim Dalında 2005-2015 yılları arasında obezite ve insülin direnci nedeniyle Metformin tedavisi alan 36 olgunun tedavi öncesi ve sonrasındaki antropometrik ve metabolik verileri karşılaştırılarak tedavi etkinliği incelendi.

Bulgular: Olgularda tedavinin 6. Ayında ağırlık SDS (Standart Deviasyon Skoru) (ort. 2.29'dan 1.8'e), VKİ (vücut kitle indeksi) (ort. 31.3kg/m^2 den 29.8kg/m^2 ye) ve VKİ SDS (ort 2.2'den 1.9'a) değerlerinde istatistiksel olarak anlamlı düşüş ($p<0,001$); VKİ değerinde 2.41±1.93kg/m^2 düşüş saptandı ($p<0,001$). Tedavi sonrasında açlık insülin, glukoz/insülin oranı; HOMA-IR ve QUICK indeksinde istatistiksel olarak anlamlı düzelme saptandı ($p<0,05$).

Sonuç: Metformin, obezite ve insülin direnci olan hastalarda 6 aylık tedavide ciddi yan etki olmaksızın ağırlık SDS, VKİ ve VKİ SDS değerlerinde ve bazı metabolik parametrelerde düzelme sağlamıştır.

Anahtar Sözcükler: adölesan, insulin direnci, metformin, obezite

Obesity and insulin resistance may cause hyperandrogenism, premature adrenarche, oligo-amenorrhea, polycystic ovary syndrome (PCOS), and hepatic steatosis in childhood and adolescence. It also increases the risk of premature death by causing metabolic syndrome, hypertension and cardiovascular diseases in adulthood (1). Some studies showed that insulin resistance and type 2 diabetes (T2DM) can be prevented by lifestyle changes and metformin treatment in adults (2-5). Metformin, is approved by the US Food Drug Administration to treat T2DM in adults and in children aged> 10 years and is recommended for medical care of adult patients with obesity (6). Metformin, is a biguanide-derived drug and stimulates activated protein kinase and suppresses hepatic glucose production, reduces intestinal glucose absorption, improves insulin sensitivity by increasing glucose uptake and use in peripheral tissues; inhibits lipogenesis in fat cells (7). Emerging evidence shows weight loss to be associated with metformin in both diabetic and non-diabetic individuals. Metformin can lead weight loss by decreasing food intake. We aimed to show the effect of metformin on weight loss, dyslipidemia and insulin resistance in a group of non-diabetic obese adolescents retrospectively.

MATERIAL and METHODS

Patients from 12 to 18 years of age who were admitted to the Pediatric Endocrinology outpatient clinic with obesity and clinical and laboratory findings compatible with insulin resistance were identified. Study patients selected whose weight control and insulin resistance data could not be improved at the end of the sixth month with the suggestions of nutrition education, exercise and lifestyle changes and Metformin treatment was used minimum six months included the study. Patients with primary endocrine pathology, syndromic obesity, who used metformin treatment for type 2 DM or impaired glucose tolerance, were excluded. The study was approved by the ethics committee of Dokuz Eylul University in light of the Helsinki Declaration (approval number; 2014/24-03). The written informed consent form was collected from parents.

The age, gender, presence of comorbidities and family history of diabetes were obtained from the file records. Tanner stage 2 breast development in girls; in boys, testicular volumes measured by orchidometers of 4 ml or more were considered as puberty. Menarche, menstrual disorder, oligomenorrhea status, acantosis nigricans and hyperandrogenism findings were recorded in the physical examination. The heigths of the cases were measured by using Harpender stadiometer to the nearest 0.1 cm and the weight was measured with SECA scale to the nearest 0.1 kg. Obesity accepted above 95 percentile for age and sex according to Turkish children (8). Blood pressure values were evaluated as percentile according to age and it was examined whether or not >95p (9). Oligomenorrhea was accepted when fewer than four periods a year in the postpostmenarcheal year and fewer than six periods a year during the second year (10). Hepatic steatosis was accepted

according to ultrasound finding or /and mild elevated ALT elevations (11). Hirsutismus was accepted score >10 according to Ferriman-Gallwey system (12). Premature adrenarche was defined as to have pubic hair before 8 year-old in girls and before 9 year-old in boys (13). Height, weight, body mass index (BMI) and standard deviation scores (SDS) of the patients were calculated before treatment and at the 3rd and 6th months of treatment (14, 15). Fasting and postprandial glucose, fasting insulin, lipid profile, thyroid functions, AST and ALT values were recorded. ISPAD criteria were used for the diagnosis of type 2 diabetes or impaired glucose tolerance (16). Insulin resistance was accepted as in the prepubertal period, HOMA-IR was 2.5 or more 4 in puberty; <0.3328 for the Quick index and <5.6 for the insulin sensitivity index (17). Fasting plasma total cholesterol (TC) and triglyceride (TG) levels and low-density lipoprotein (LDL) were determined based on age and sex> 95 percentile values (18) and metabolic syndrome criteria were used for high density lipoprotein (HDL) (19). Metformin dose, duration of use, drug-related side effects (nausea, vomiting, abdominal pain, lactic acidosis, etc.) were recorded.

Metformin treatment was initiated in 80 cases in our clinic. 28 cases were excluded with at least one of the exclusion criteria and 16 patients were excluded due to incomplete file records. The data of the remaining 36 cases were recorded, and the data of 23 patients who used the treatment regularly were evaluated before and after the treatment.

Statistical Analysis

Data were evaluated with SPSS 21.0 program. Descriptive statistical method was used for the mean of group data and chi-square test was used for comparison of group rates. Pre and post treatment data of the group were compared with non-parametric Wilcoxon test. Data were given as mean +/- SD or median, $p < 0.05$ was considered statistically significant.

RESULTS

The study consisted of a population of 36 patients with 72.2% (n= 26) girls and 22.8 % (n= 10) boys. The mean age was 13.8 ± 1.8 years (12-17.8 years). On admission, all of the patients had obesity and insulin resistance, and had oligomenorrhea (n=7), hepatic steatosis (n= 5), hirsutismus (n= 3), and premature adrenarche (n= 1). All patients had normal fasting glucose normal postprandial glucose and/or normal oral glucose tolerance test (OGTT).

In 14% of the cases, parents and/or their siblings, 39% had a history of Type 2 DM in grandparents. In two cases (5.6%), the mother had a history of gestational diabetes. Acanthosis nigricans was found in 50% (n= 18) of the patients on physical examination. 72.2% of the patients with acanthosis were girls. However, no statistical difference was found according to gender ($p > 0.05$). Blood pressure was normal in all cases. 94.4% (n= 34) of the cases were more advanced than stage 1 puberty. Of the 14 menarche cases, 78.6% (n= 11) had menstrual irregularity.

The anthropometric measurement data of the cases before and after the treatment are shown in Table 1. The patients' weight had decreased by an average of 3.6 kg during the treatment. Mean weight, weight SDS, BMI, BMI percentile and BMI SDS were improved significantly (Table 1).

Fasting insulin levels, fasting glucose/insulin ratio, HOMA-IR index and Quick index values without decreasing glucose levels improved significantly in all cases with metformin treatment (Table 1). Insulin resistance, which was present according to at least two parameters in all patients before treatment, showed a significant improvement after treatment (Table 2).

Table 1. Comparison of the characteristics of the patients before and after treatment

	Pre-treatment (n= 23)	**Post-treatment (n= 23)**	*p**
Weight SDS	2.2 ±0.8 (2.29)	1.9± 0.9 (1.8)	**<0.001**
Height SDS	0.4 ± 1.5 (0.7)	0.3 ± 1.5 (0.50)	0.130
BMI (kg/m²)	32.3 ± 6.0 (31.3)	29.9 ± 6 (29.8)	**<0.001**
BMI SDS	2.1 ± 0.4 (2.2)	1.8 ± 0.6 (1.9)	**<0.001**
Fasting glucose (mg/dL)	84.4 ± 11.8 (87)	86.3 ± 8.6 (87)	0.465
Fasting insulin (μIU/mL)	26.3 ± 13.2 (22.8)	18.1 ± 8.0 (15.4)	**0.005**
Fasting glucose/ fasting insulin	3.9 ± 1.6 (3.7)	5.7 ± 2.5 (5.5)	**0.004**
HOMA-IR	5.6 ± 3.2 (4.7)	4.0 ± 2.0 (3.4)	**0.015**
Quick index	0.30 ± 0.02 (0.3)	0.32 ± 0.02 (0.3)	**0.014**

*Data are given as mean ± SD (median). *Wilcoxon test*

BMI, Body mass index

Table 2. Rate of insulin resistance

	Pre-treatment	**Post-treatment**	**p***
Fasting glucose/ fasting insulin	% 91.7	% 33.3	**0.021**
HOMA-IR	% 69.4	% 39.1	**0.039**
Quick indeks	% 91.7	% 38.9	**0.039**

**McNemar test*

Pre and post treatment values of 14 patients with complete lipid profile data were compared. Before treatment, high plasma TG was found in 36% (n= 5), high TC in 14% (n= 2), and LDL level above 95 percentile in 14% (n= 2); HDL level was low in 21% (n= 3). In the sixth month of treatment, high plasma TG was found in 36% (n= 5), high TC in 14% (n= 2), and LDL levels above 95 percentile in 7% (n= 1); HDL level was low in 28% (n= 4) cases. The differences observed in all four parameters were not statistically significant (p> 0.05) (Table 3).

Table 3. Lipid profile of cases

	Pre-treatment (n= 14)	**Post-treatment (n= 14)**	**p***
TG (mg/dL)	125,8±66.7 (102.5)	122.8±73.8 (90)	0.777
TC (mg/dL)	169.9±27.2 (162.5)	166.1±31 (153)	0.300
LDL Chol (mg/dL)	99.4±21.0 (91)	96.3±23.9 (91.5)	0.232
HDL Chol (mg/dL)	43.9±10 (42.5)	45.1±8.3 (43.5)	0.683

*Data are given as mean ± SD (median). *Wilcoxon test*

TG, triglyceride; TC, total cholesterol; LDL Chol, low density lipoprotein cholesterol; HDL Chol, high density lipoprotein cholesterol.

There were no significant differences in ALT and AST levels in the 5 patients with hepatic steatosis before treatment (p> 0.05). There was no significant change in the hepatic steatosis stage detected by ultrasonography before treatment. There was no significant change in thyroid function tests before and after treatment.

Metformin treatment was started at 500 mg/day and the maximum dose was given as 2000mg/day with an increase of 500 mg weekly. It was determined that 38% (n= 22) of the patients discontinued their treatment before three months and 55% of the patients continued their treatment for 12 months or more. No serious side effects were observed in any of the cases. One patient who received 2x250 mg had abdominal pain and nausea; in one case, diarrhea was observed while taking 2x1000 mg but resolved without stopping the treatment.

DISCUSSION

The high number of female patients in the study group was consistent with the fact that most of the patients who presented to our clinic with obesity were female. The reason may be that girls and their families are more disturbed by the body perception caused by obesity and that girls are less involved in out-of-home life and sports activities due to sociocultural habits. Majority of the cases had a family history of T2DM. In the literature, the presence of T2DM in the family has been shown to correlate with insulin resistance. In the study of Arslanian et al. (20) lower insulin sensitivity was found in patients with T2DM in the family by hyperinsulinemic euglycemic clamp test. In a study conducted in adults, fasting insulin levels and HOMA IR values were found to be higher in patients with familial T2DM (21).

Acanthosis nigricans is a skin finding of insulin resistance, was present in 50% of our cases. It is related duration and severity/intensity of insulin resistance. In a randomized controlled study on obese children and adolescents with insulin resistance, the authors were defined 58.9 % in study group and 52.9 % in control group presented acanthosis nigricans (22) it has been reported in the literature that the risk of T2DM is increased in patients with acanthosis nigricans (23). Ice et al. (24) demonstrated the presence of three criteria of metabolic syndrome (insulin resistance, increased BMI, high blood pressure or dyslipidemia) in 49% of children with acanthosis nigricans.

In our study, 34 of 36 cases were in puberty. It is known that there is a decrease in insulin sensitivity up to 25% -50% in puberty, especially during pubertal growth spurt (25). In a longitudinal study, Goran et al. (26) showed a 32% decrease in insulin sensitivity in children reaching Tanner stage 3.

The relationship between obesity and insulin resistance with oligo-amenorrhea, polycystic ovary and infertility is well known (27). We thought that menstrual cycle irregularity, which was detected in 78.6% of our cases, could be related to maturation of ovulation cycle in puberty as well as obesity and insulin resistance.

In our study, we found statistically significant decrease in weight SDS, BMI and BMI SDS values after six months of metformin treatment. The mean BMI value decreased by 2.41 ± 1.93kg/m^2. There are many randomized controlled trial and meta-analysis regarding the effects of metformin in pediatric obesity. Some of them claimed no effect on insulin resistance and BMI (28) but many other randomized controlled studies showing a decrease of 0.16 - 3.2 kg/m^2 with metformin treatment in obese children and adolescents (29-33). The successful outcome in our study may be related to case selection and treatment adherence. In literature, major changes seen in BMI were reported in the third and fourth months of treatment and the change was less between sixth and twelfth months (30, 31). In a long-term following study (36 months) authors claimed lack of compliance and insufficient dose may explain the differences in long-term effects between adolescents and adults (34).

Recently, the growth differentiation factor-15 (GDF-15), a member of the transforming factor beta superfamily, has been identified as a key mediator of metformin-induced weight loss. Metformin increases the secretion of GDF-15, which binds exclusively to glial cell-derived neurotrophic factor family receptor alpha-like. This gut-brain cytokine works as a prominent player in reducing food intake and body weight in health and disease, like anorexia nervosa and cancer (35).

There was a significant decrease in fasting insulin levels without decrease in fasting blood glucose levels in our patients who received metformin treatment and a statistically significant improvement was observed in all three parameters evaluating insulin resistance. In other words, insulin resistance improved in all patients with insulin resistance according to at least two parameters prior to treatment, in more than half of the patients after the sixth month of treatment. In the literature, many placebo-controlled studies have clearly demonstrated the effect of metformin on fasting insulin levels (30). In contrast, there is a study that does not find a significant decrease in HOMA-IR index (31).

Triglyceride and total cholesterol levels of our treated patients decreased slightly with treatment and increased HDL levels, but these changes were not statistically significant. Metformin, which is known to inhibit lipogenesis in fat cells, may have a direct effect on lipid profile or may be this effect associated with weight loss. Several studies have shown that total cholesterol levels decreased slightly with metformin treatment (30, 34-36). Some studies showing limited or significant decrease in triglyceride levels but they had lower quality of evidence. In our study group, the number of patients with dyslipidemia decreased after metformin treatment, but the difference was not statistically significant. This may be related to the small number of cases.

Metformin is usually well tolerated. However, transient mild gastrointestinal adverse effects such as nausea, vomiting, abdominal pain, flatulence, and diarrhea are common especially during the initiation of metformin therapy (30, 31). In our study, no serious side effects were observed in our patients who used metformin treatment. Metformin is well tolerated in most patients, but moderate gastrointestinal side effects such as nausea, constipation and abdominal pain were observed. These effects are reported to occur between the ages of 6-12 and in the first month of treatment (30). Cases of lactic acidosis reported in the literature have occurred after large amounts of suicidal intake (37). In a ten years retrospective analysis from an intensive care unit of University of Lille, France, authors find forty-two patients; 13 voluntary intoxication and 29 incidental overdoses (38). The incidence of Metformin-Associated Lactic Acidosis (MALA) is rare. The estimated rate of MALA is 2 to 9 case per 100.000 person-years (39). The high rate of discontinuation of treatment is probably due to these transient mild gastrointestinal side effects. We should educate our patients more about the side effects and can tolerate over time when starting treatment.

In conclusion, Metformin was found to be effective in increasing insulin sensitivity by decreasing fasting insulin levels in obese children and especially adolescents with insulin resistance, and limited but significantly effective in weight loss.

Limitations of the study

Metformin has no approval use for obesity in pediatric age group without T2DM or impaired glucose

tolerance. For this reason, the study design was retrospective and sample size was small. Our results should be confirmed by additional research involving more patients in childhood.

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