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Original Article

Long-term follow-up of non-diabetic obese children and adolescents treated with metformin

Metformin ile tedavi edilen non-diyabetik obez çocuk ve adolesanların uzun sureli izlemi

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ABSTRACT

Aim: Childhood obesity is an important public health problem with increasing prevalence. Type 2 diabetes mellitus(T2DM) is strongly associated with obesity and metabolic syndrome. Adressing obesity and insulin resistance by drug treatment represents a rational strategy for the prevention of T2DM. The aim of our study was to evaluate the one year metformin treatment'slong-term effectiveness in children and adolescent.

Material and Methods: Patients who were diagnosed with obesity (VKİ>+2 SDS) and found to have insulin resistance (total insulin at OGTT >300 mIU/ml and homa-IR >3.4)and other obesity co-morbidities, aged between 10-18 years, treated with metformin in addition to lifestyle change for a year and with regular follow-up for a minimum of 2 years after metformin treatmentin our clinic were included inthe study.

Results: A total of 12 cases including 8 girls with a mean age of 13.2±2.1 years and mean follow-up duration of 3.9±1 years were included in the study. While the body mass index (BMI) of the cases at presentation was 31.2±5.6 kg/m2 and BMI-SDS was 2.7±0.7, the BMI-SDS value after one year of metformin treatment was found to have regressed to 1.9±1 (p:0.04), and the BMI-SDS value two years after the interruption of metformin treatment had increased to 2.1±1.04 but was not as high as the period before metformin treatment (p:0.033).

Conclusion: One-year metformin treatment improved the BMI SDS and homa-IR values of the obese children and this improvement decreased but continued in the second year after the discontinuation of the treatment.

Keywords: obesity; insulin resistance; childhood

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ÖZ

Amaç: Çocukluk döneminde obezite artan sıklıkla izlenen önemli bir halk sağlığı problemidir. Tip 2 Diyabetes mellitus (T2DM) obezite ve metabolik sendrom ile güçlü ilişki içindedir. Tip 2 DM 'nin önlenmesi için obezite ve insulin direncini hedef alan ilaç tedavileri rasyonel bir strateji olarak görülmektedir. Çalışmamızın amacı bir yıl süre ile metformin tedavisi alan çocuk ve adolesanlarda bu tedavinin uzun dönem etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Kliniğimizde obezite (VKI>+ 2SDS) tanısı alan ve insulin direnci olan (OGTT'de total insulin düzeyi >300 mIU/ml ve homa IR >3,4) ve diğer obezite ilişkili komorbiditeleri bulunan, yaşları 10-18 arası değişen, yaşam tarzı değişikliği ile birlikte bir yıl süre ile metformin tedavisi alan ve ardından en az iki yıl süre ile takip edilen hastalar dahil edildi.

Bulgular: Çalışmaya 8' i kız , ortalama yaşı 13,2±2,1 yıl olan ve ortalama izlem süresi 3,9±1 yıl olan toplam 12 dahil edildi. Başlangıçta olguların vücut kitle indeksi (VKİ) 31,2±5,6 kg/m2 ve VKİ-SDS'i 2,7±0,7 iken bir yıllık metformin tedavisi ile VKİ-SDS'inin 1,9±1 (p:0,04) ' e gerilediği, iki yıl süre ile metformin tedavisi kesilen olguların VKİ-SDS' inin 2,1±1,04 (p:0,033)' e yükseldiği ancak metformin tedavisi öncesi kadar yüksek olmadığı görüldü.

Sonuç: Bir yıllık metformin tedavisinin obez çocuk ve adolesanlarda VKİ-SDS ve Homa-IR değerlerinde düzelme sağladığı, bu düzelmenin tedavi kesiminden sonraki ikinci yılda da azalmakla birlikte devam ettiği saptandı.

Anahtar kelimeler: obezite; insülin direnci; çocukluk dönemi

Introduction

Obesity is currently the leading topic of discussion related to child health due to its increasing prevalence and the low treatment success rate [1]. More than 20% of the children living in the USA, Europe, Australia and East Mediterranean are overweight or obese [2]. An increase was found in almost all countries in a study evaluating the changes in obesity prevalence worldwide between 1980 and 2005 in school-age children from 25 countries and pre-school age children from 42 countries [3].

A significant increase in insulin resistance was observed in children and adolescents simultaneous with the increase in obesity incidence in childhood. A relationship is known to be present between insulin resistance and obesity and the obesity-related metabolic and cardiovascular problems. Therefore, the treatment of children and adolescents with insulin resistance in the early stages is important. Patients who are not treated progress to type 2 diabetes mellitus (T2DM), and atherosclerosis develops at an early stage [2].

Lifestyle change is the treatment strategy to be used first in the treatment of obesity and obesity-related complications[4]. Data obtained from a large number of studies show that changes made in the lifestyle enables weight loss, increases insulin sensitivity and decreases the risk of T2DM development. However, results of lifestyle changes can be disappointing in the long term and the obesity and T2DM incidences continue to increase [5]. Pharmacologic agents that will prevent T2DM by preventing obesity and insulin resistance in obese children and adolescents are therefore required. Park et al published a meta-analysis evaluating the efficiency of metformin treatment in obese children without a T2DM diagnosis in 2009. They concluded that metformin treatment reduced the body mass index (BMI) and decreased the homeostasis model assessment of insulin resistance (homa-IR) score [6]. Other studies evaluating the effect of metformin have been published after this study [7-15]. However, the effectiveness and safety of metformin in obese children with a normal glucose metabolism is still contradictory. There is also no study reporting long-term follow-up after treatment.

The aim of our study was to evaluate the effectiveness of long-term metformin treatment in children and adolescent patients who were treated with metformin for a year in addition to lifestyle changes.

Material and Methods

Patients who were diagnosed with obesity at Clinics of Pediatric Endocrinology, Health Sciences University, Dr Sami Ulus Obstetrics and Gynecology, Children's Health and Disease, Health Implementation and Research Center were screened retrospectively. The diagnosis of obesity was made with a body weight over +2 SD of the body weight for age and gender. Patients who had undergone an oral glucose tolerance test (OGTT) and found to have insulin resistance (total insulin at OGTT>300 mIU/ml and homa-IR>3.4). In this patients,obesity

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related problems such as abnormal liver function test and/or fatty liver, hypertension, dyslipidemia, metabolic syndrome (according to WHO criteria) were present. Patients whose aged between 10 and 18 years, and treated with 2*425 mg (total 850 mg/day)metformin bd in addition to lifestyle change for a year were included in the study. The study group consisted of 12 cases without a T2DM diagnosis or additional medical problems, who had no previous history of drug use for insulin resistance or drug use that could cause obesity, and with regular follow-up for a minimum of two years after metformin treatment of one year. Fasting glucose and fasting insulin level were used to measure the homa-IR value of the cases during the follow-up. Anthropometric measurements, fasting blood sugar, insulin values, hba1c, homa-IR, results and the changes in these parameters during follow-up were recorded. Local ethics committee approved the study and informed consent was obtained from participant(s)

Results

A total of 12 cases including 8 girls with a mean age of 13.2±2.1 years and mean follow-up duration of 3.9±1 years were included in the study. While the body mass index (BMI) of the cases at presentation was 31.2±5.6 kg/m2 and BMI-SDS was 2.7±0.7, the BMI-SDS value after one year of metformin treatment was found to have regressed to 1.9±1 (p:0.04), and the BMI-SDS value two years after the interruption of metformin treatment had increased to 2.1±1.04 but was not as high as the period before metformin treatment (p:0.033). The mean homa-IR value measured at the beginning was 4.8±1.66 and was found to have regressed to 2.5±1.5at the end of the 1st year (p:0.008). Although it increased to 3.5±1.6 2 years after the interruption of metformin treatment, it was still lower than the homa-IR value before metformin treatment was started (p:0.021). Table 1 presents the anthropometric measurements, fasting blood sugar, insulin, hba1c, homa-IR at the first year of the treatment, and one year and two years after the discontinuation of metformin.

Only one case had symptoms related to the gastrointestinal system during metformin treatment but these symptoms regressed rapidly. No serious side effects that could cause drug discontinuation were observed.

Table 1. Anthropometric measurements, fasting blood sugar, insulin, Hba1C, homa-IR results and evaluated with these parameters of the cases before metformin, at the first year of metformin treatment, and one and two years after the discontinuation of metformin

	Pre-metformin	Metformin treatment 1st Year	1st year after the discontinuation of metformin	2nd year after the discontinuation of metformin
BMI	31.2±5.6	28.4±5.8	28.3±6.1	30.4±6.4
BMI-SDS	2.7±0.7	1.9±1	1.98±1.05	2.1±1.04
Fasting glucose (mg/dl)	87.5±0.8	85.3±8.8	85.6±5.4	85.3±4.3
Fasting insulin (µIU/ml)	21.9±6.8	11.5±6.9	14.1±3.6	16.7±7.7
Homa-IR	4.7±1.7	2.5±1.5	3±0.8	3.5±1.6
Hba1C (%)	5.3±0.35	5.1±0.26	5±0.37	5.1±0.25

Discussion

Obesity in childhood and the adolescent period constitutes an increased risk for many metabolic complications such as insulin resistance, impaired glucose tolerance and T2DM. Insulin resistance develops on the basis of these disorders and is the most common metabolic change related to obesity [15]. Insulin leads to a biological response that is lower than expected in insulin resistance. There is especially a decrease in the ability of insulin to stimulate glucose use by muscle and fat tissue and suppress the production and secretion of hepatic glucose [16]. Type 2 diabetes mellitus is known to develop at the final stage in adults as a result of the progressive impairment in insulin resistance and secretion. The situation in children and adolescents is not clear. However, a study has indicated the need to start treatment in children at an early stage in order to prevent the development of diabetes as a result of insulin resistance and beta cell dysfunction [17].

Lifestyle change is known to provide weight loss and increase insulin sensitivity and therefore decrease T2DM development [5]. However, the effectiveness of life style change is known to depend on the content of the program and to be subjective with limited long-term success [12]. Metformin efficiency is evaluated as an important treatment alternative in obese, non-diabetic cases due to its effectiveness, reliability, and metabolic and cardiologic benefits [5]. Success has been reported regarding weight loss after 6-12 months of metformin treatment in most of the relevant studies [7-10,12-14]. There are also studies that report an improvement in fasting glucose and insulin resistance [Homa-IR and the quantitative insulin sensitivity check index (QUICKI)[7-9,11]. These studies indicate

in general that metformin is anti-obesity agent with moderate effectiveness [5,7-14]. Our clinical observation is that lifestyle change with metformin treatment is more successful than lifestyle change alone. One of the reasons may be that the children disregard the diet when recommended by itself but taking it more seriously when recommended together with a drug. Another factor may be the easy adaptation of the patients to the changes regarding nutrition because of the gastrointestinal side effects of metformin treatment.

Studies on the effectiveness of metformin treatment in childhood and the adolescent period have evaluated relatively short-term metformin treatment. A reduction in BMI-SDS and homa-IR was seen with 12 months of metformin treatment in our study. Long-term follow-up results after metformin treatment are not available in childhood and the adolescent age group. Data regarding results of the cases that were followed-up only for one year after metformin treatment were reported by Wilson et al. The positive effects on weight obtained with metformin treatment were reported to disappear after the end of one year[12]. We were able to obtain two-year follow-up results of the cases after metformin treatment in our study and the positive effects were reported to continue although decreased.

The most common side effects in metformin treatment are gastrointestinal problems such as abdominal pain and diarrhea. However, these symptoms usually resolve spontaneously within a short time. Lactic acidosis is the most serious side effect. It has been reported rarely in adult studies but there is no case reported in childhood and the adolescent period [2].Gastrointestinal symptoms occurred in one of the cases in our study but did not require metformin treatment to be interrupted and the symptoms regressed in a short time. No other side effect related to lactic acidosis or metformin use was observed in any of our cases.

One of the important limitations of our study is its retrospective design and the inability to homogenize the lifestyle changes that were recommended. Another limitation is the limited number of cases that could be included in the study. Another cause of potential difficulties in the comparison of the results from previous studies with our results is the different doses of metformin used. However, there is no relationship between the metformin dose and the BMI decrease [5]. We used a minimum metformin dose of 425 mg bd for effectiveness in our study.

Conclusion

We determined in our study that one-year metformin treatment improved the BMI SDS and homa-IR values of the obese children and this improvement decreased but continued in the second year after the discontinuation of the treatment. A severe side effect of metformin was not observed in any case. We conclude that metformin treatment has a positive effect on BMI and insulin resistance in obese children and adolescents and its effects on metabolic syndrome needs to be evaluated with larger case studies.

Declaration of conflict of interest

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References

1. McDonagh MS, Selph S, Ozpınar A, Foley C. Systematic reviewof the benefits and risks ofmetforminin treating obesity in children aged 18 years and younger. JAMA Pediatr 2014; 168: 178-84
2. Ho M, Garnet SP, Baur LA. Childhood Obesity and Insulin Resistance: How should It be Managed?.Curr Treat Cardio Med 2014; 16: 351
3. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. IntJ PediatrObes, 2006; 1: 11-25
4. van der Aa MP, Elst MA, van Mil EG, Knibbe CA, van der Vorst MM. METFORMIN: an efficacy, safety and pharmacokinetic study on the short-term and long-term use in obese children and adolescents - study protocol of a randomized controlled study. Trials 2014; 15: 207
5. Brufani C, Crino A, Fintini D, Patera IP, Cappa M, Manco M. Systematic Review of Metformin Use in Obese Nondiabetic Children and Adolescents. Horm Res Paediatr 2013; 80: 78-80
6. Park MH, Kinra S, Ward KI,White B, VinerRM. Metformin for obesity in children and adolescents: a systematicreview. Diabetes Care 2009; 32: 1743-45
7. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics 2001; 107: 55
8. Srinivasan S, Ambler GR, Baur LA, Garnett SP, Tepsa M, Yap F, Ward GM, Cowell CT. Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. J ClinEndocrinolMetab 2006; 91: 2074–80
9. Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. J Pediatr Endocrinol Metab 2008; 21: 339–48

10. Clarson CL, Mahmud FH, Baker JE, Clark HE, McKay WM, Schauteet VD, Hill DJ. Metformin in combination with structured lifestyle intervention improved body mass index in obese adolescents, but did not improve insulin resistance. Endocrine 2009; 36: 141–46
11. Wiegand S, l'Allemand D, Hübel H, Krude H, Bürmann M, Martus P, Grüters A, Holl RW. Metformin and placebo therapy both improve weight management and fasting insulin in obese insulin resistant adolescents: a prospective, placebo-controlled, randomized study. Eur J Endocrinol 2010; 163: 585–92
12. Wilson D.M, Abrams SH, Aye T, Lee PDK, Lenders C, Lusting RH, OsganianSV, Feldman HA. Metformin extended release treatment of adolescent obesity. Arch PediatrAdolescMed 2010; 164: 116-23
13. Rynders C, Weltman A, Delgiorno C, Balagopal P, Damaso L, Killen K, Mauras N. Lifestyle intervention improves fitness independent of metformin in obese adolescents. Med Sci Sports Exerc 2012; 44: 786–92
14. Mauras N, DelGiorno C, Hossain J, Bird K, Killen K, Merinbaum D, Weltman A, Damaso L, Balagopal P. Metformin use in children with obesity and normal glucose toleranceeffects on cardiovascular markers and intrahepatic fat. J PediatrEndocrinolMetab 2012; 25: 33–40
15. Weiss R, Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. DiabetesCare 2008; 31: 310-16
16. MatthaeiS, Stumvoll M, Kellerer M, Haring HU. Pathophysiology and pharmacological treatment of insulin resistance. Endocr Rev 2000; 21: 585-618
17. Cali AM, Man CD, Cobelli C, Dziura J, Seyal A, Shaw M, Allen K, Chen S, Caprio S. Primary defects in ß-cell function further exacerbated by worsening of insulin resistance mark the development of impaired glucose tolerance in obese adolescents. Diabetes Care 2009; 32: 456-61