

Clinical Picture at Attendance and Response to Flexible Family-Based Low-Carb Life Style Change in Children With Obesity

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Abstract: *Aim:* The study aims 1) to determine the clinical status of obese children at the admittance to the pediatric endocrinology referral center 2) to investigate the efficiency and compliance of the low-carb diet in a pediatric population with or without exercise, metformin

Material and Methods: All subjects with the complaint of obesity and BMI percentile >95 were recruited from January 2012-August 2014. We evaluated basal retrospectively, recommended low carbohydrate family-wide eating practice and exercise to all, and metformin to selected cases, and recorded Self-reported adherence at first, third, sixth, and twelfth months.

Results: Thirty-six subjects used metformin with a higher ratio of weight loss (90.0%, $p=0.010$) without a difference in the number of lost kilograms. In 160 cases without metformin; diet only, exercise only, and both diet and exercise groups lost weight significantly according to neither diet nor exercise group (OR:12.08, 95% CI 3.93-41.66, $p<0.001$; OR:3.04, 95% CI 1.18-7.84, $p=0.022$ and OR:32.80, 95% CI 7.14-150.77, $p<0.001$ respectively). Exercise plus diet (95.3%, $p=0.002$) and only diet (88.9%, $p=0.023$) were even more efficient than exercise alone (65.5%). In the twelfth month, 13.8% were on follow-up.

Conclusion: Obesity gives rise to metabolic complications in the very early stages. A low carbohydrate diet proved to be acceptable and useful. Long-term consistency remains a challenge.

Keywords: Children, Complications, Low-carbohydrate diet, Metformin, Obesity.

INTRODUCTION

The World Health Organization defines obesity as a disorder of excess body fat associated with an increased risk of disease [1]. The prevalence of obesity is rising [2]. Between the ages of 6-19, approximately 1 in 5 children in the U.S. are currently obese; % 4-7 of these children suffer from severe obesity. In Turkey, obesity rates in children are reported between 2.2-7.8 % in different cohorts [3-5]. In a previous study conducted in our geographic region, obesity prevalence was 6.1% [5].

Untreated obesity increases the risk of metabolic disturbances, obstructive sleep apnea, cardiovascular diseases, and orthopedic problems [6,7]. Obese children may present with mixt features of type 1 and type 2 diabetes [8]. Psychosocial issues, especially the risk of discrimination, deserve interest as well [9,10].

Primary prevention (preventive strategies for the individual), secondary prevention (screening), and tertiary prevention (treating obesity and its complications) are components of the fight with

pediatric obesity. Increased physical activity, decreased sedentary behaviors, dietary approaches, medicines, and surgery are the spectrum of treatment choices. If supervised lifestyle intervention fails, therapeutic approaches, including pharmacotherapy, must be considered [11]. Metformin has the advantages of decreasing appetite and fat stores, improving lipid profiles, and is recommended in adolescents with insulin resistance [11,12]. Besides, smart approaches targeting individuals (devices, software) and groups (motivation using group dynamics) were induced [13,14]. There is currently a search for the appropriate level of health service for intervention worldwide [15]. In our country, the pediatric endocrinology clinic is the place of choice for the intervention.

This study aimed to determine the general characteristics of childhood obesity at the pediatric outpatient clinic setting during admittance and follow-up and criticize our treatment approaches. The study has combined retrospective and prospective set-up.

MATERIALS AND METHODS

Our pediatric endocrinology department is a unique one in 6 provinces throughout the geographic region. Officially subjects aged 0-18 years may be accepted.

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All cases complaining or referred to obesity between January 2012-August 2014 were recruited when BMI \geq 95th percentile [16]. We excluded Cushing, hypothyroidism, growth hormone deficiency, and syndromic cases. We collected basal data collected according to the clinic's routine, i.e., detailed personal and family history, age at onset of obesity. We also evaluated the development of excess weight over time, parental weight status, physical examination, laboratory results of fasting blood sampling retrospectively using electronic records. Routine blood count and fasting biochemistry and hormones are checked in every case, at least once. All medical records, including laboratory values, detailed history, height measured by Harpenden stadiometer, and weight by an electronic scale (SECA 767 physician scale) with light clothes, puberty staging according to Tanner, full physical examination are accessible for the departments' staff through the hospitals medical portal. BMI was as kg/m². Tanner scale defines physical development (primary, secondary sex characteristics) [17]. The BMI reference graphs adapted to Turkish children were used [18]. These data were transferred by the same physician to a worksheet and controlled by the department's supervisor.

We used BMI Z score to compare weight data between children of different ages at the first visit. In the following months, we compared weight change between groups, metformin versus no metformin, diet versus no diet, the exercise versus no exercise, and diet plus exercise versus exercise alone. Follow-up data about weight measurement and a simple verbal questionnaire about self-reported diet and activity compliance were collected prospectively by the same physician.

Laboratory Methods

Venous blood samples were obtained from all patients between 08:00-10:00 after an overnight fast. Fasting blood glucose, lipids, and liver enzymes were measured by chemiluminescence, HbA1C was measured by high-performance liquid chromatography (HPLC). Insulin, thyroid hormones, and cortisol were measured by electrochemiluminescence.

Management

We recommend a change in eating and shopping habits of the family towards a low carbohydrate diet and no caloric restriction. In the first visit, an interview about carbohydrate-containing foods that are subject to

limitation is done. Also, samples of the right foods rich in protein, fats from olive oil, nuts, dairy products, meats, and vegetables are given. Cholesterol and saturated fat (except for margarine) have to be consumed ad libitum as well. No strict food plan was offered, except for a two-page sheet containing every possible positive choice for meals and snacks and samples of foods rich in carbohydrates. The whole family was advised to change the eating behavior to explain that this is not a diet, a life-long healthy eating practice! Theoretically, the recommended carbohydrate intake constitutes 20-40% of total energy intake. Also, we suggested no number for meals and snacks, nor any quantities (i.e., 2-6 meals are acceptable daily). When the child fails to do the perfect, any little difference in attitudes is welcome, and the family has to change the home attitudes; pushing the child for dieting is discouraged. We allowed only the child's social eating occasions to protect peer relations. Also, performing at least 30 minutes of daily exercise is recommended. These exercises included skip rope, walking, running, playing basketball, or volleyball three to five times a week. At the first visit, only for cases with insulin resistance and self-reported fear of noncompliance (both should be together) was initiated metformin treatment. In the follow-up, metformin was prescribed to patients failing to lose weight and having insulin resistance. An initial dose of metformin was 1000 mg/day taken during dinner.

Institutional Ethics Committee of Duzce University Faculty of Medicine approved this study (Approval number: 2019/50).

Evaluation and Statistics

Homeostasis model assessment- insulin resistance (HOMA-IR) was used to evaluate insulin resistance and obtained by calculating [HOMA-IR: (fasting glucose (mg/dL) X fasting insulin (U/l))/405]. The cut-off was 2.5 for prepubertal and 3.16 for pubertal children [19]. We used age, and sex-adjusted centiles published by Neal were used for lipids [20]. Fasting blood sugar \geq 100 or HbA1c \geq 6 was considered abnormal glucose homeostasis, and diabetes if \geq 126 and \geq 6.5, respectively [21].

Waist circumference, blood pressure, and oral glucose tolerance are our routine but not included in this analysis.

We recorded that self-reported diet and exercise adherence was recorded at baseline, at the third, sixth,

Table 1: Baseline Characteristics

Age mean±SD (range)	10.4±3.7 (0.3-17.9)		
Sex n (%)	Female	206 (58.5)	
	Male	146 (41.5)	
BMI Z Score mean±SD	2.7±0.9		
Puberty Tanner Stage n (%)	1	163 (46.4)	
	2	55 (15.6)	
	3	54 (15.3)	
	4	13 (3.7)	
	5	67 (19.0)	
Obesity in the family (n=271) n (%)	none	60 (22.1)	
	first degree	151 (55.7)	
	others	60 (22.1)	
FPG (mg/dl) n (%)	<100	288 (81.8)	
	100-126	62 (17.6)	
	≥126	2 (0.6)	
HbA1c (n=345) n (%)	<6	297 (86.1)	
	6-6.5	38 (11.0)	
	≥6.5	10 (2.9)	
HOMA-IR Median [25%-75%]	2.93 [1.88-4.91]		
HOMA-IR by puberty n of high/total (%)	Prepubertal (>2.5)	72/160 (45.0)	
	Pubertal (>3.16, Tanner 2-5)	125/185 (67.6)	
	Tanner 5 subgroup	57/66 (86.4)	
	Overall	197/345 (57.1)	
Triglyceride percentile > 95 by age and sex n/total (%)	Age	Female	Male
	1-4	3/22 (13.6)	2/5 (0.4)
	5-9	19/69 (27.5)	32/53 (60.4)
	10-14	40/92 (43.5)	33/74 (44.6)
	15-19	7/22 (31.8)	3/14 (21.4)
	Subtotal	69/205 (33.7)	70/146 (47.9)
	Total	139/351 (39.6)	
LDL percentile > 95 by age and sex n/total (%)	5-9	1/62 (1.6)	4/51 (7.8)
	10-14	7/49 (14.3)	11/66 (16.7)
	15-19	1/22 (4.5)	2/18 (11.1)
	Subtotal	9/133 (6.8)	17/135 (12.6)
	Total	26/268 (9.7)	
HDL percentile < 10 by age and sex n/total (%)	5-9	12/62 (19.4)	9/51 (17.6)
	10-14	18/49 (36.7)	8/66 (12.1)
	15-19	5/22 (22.7)	4/17 (23.5)
	Subtotal	35/133 (26.3)	21/134 (15.7)
	Total	56/267 (21.0)	
Any dyslipidemia by age and sex n/total (%)	1-4	3/22 (13.6)	2/5 (0.4)
	5-9	25/63 (39.7)	32/51 (62.7)
	10-14	46/87 (52.9)	39/72 (54.2)
	15-19	9/22 (40.9)	6/12 (50.0)
	Subtotal	83/194 (42.8)	79/140 (56.4)
	Total	162/334 (48.5)	
High liver enzymes n/total (%)	8/352 (2.3%)		

Abbreviations: BMI (Body mass index), FPG (fasting plasma glucose), HOMA-IR (Homeostasis model assessment- insulin resistance), LDL (low-density lipoprotein), HDL (High-density lipoprotein).

and twelfth months of follow-up prospectively. Comparisons in subgroups in aspects of performing diet or not; receiving metformin or not; performing at least 30 minutes daily exercise or not, and performing exercise plus diet or did the only activity.

Continuous data were summarized as mean±standard deviation, median (25%-75%), and categorical data were summarized as frequency and percentiles. Mann-Whitney U test was used to compare groups, and Chi-square and Fisher's exact test was used to analyze the association between categorical variables. Logistic regression analyses were done to examine the effects of variables on weight loss. Statistical analyses were done by PASW v.18 statistical package, and p values less than 0.05 were considered significant.

RESULTS

A total of 352 children were included. There were 41 (11.6%) children in the youngest age group (0-6 years), 311 (88.4%) were between 6-18 years, girls were predominant (58.5%), 163 (46.3%) were prepubertal, 1 (0.3%) had delayed puberty, 14 (4.0%) had precocious puberty. Ten children under age 3 had BMI values > 20 (Table 1).

Abnormal glucose homeostasis was detected in 111 cases (31.5%), 63 regarding fasting glucose, 47 HbA1c, one both. One subject had fasting glucose ≥ 126 mg/dl, nine had HbA1c $\geq 6.5\%$, and one had both classified as diabetes (3.1%). We found insulin resistance in 57.1%, hypertriglyceridemia 39.5%, decreased HDL in 21.0%, high liver enzymes in 2.3%, lipid abnormality in 48.5%, and any biochemical abnormality 81.3% (Table 1).

Out of 352 patients, 63 (17.9%) used metformin. A total of 200 subjects could be evaluated for further analysis because of information losses about diet-exercise and or drop out from follow-up (Figure 1).

Of the 200 subjects (116 girls and 84 boys) prospectively questioned for diet and exercise, 41 reported adherence to the only diet, of which 23 (19.8%) were girls and 18 (21.4%) were boys ($p=0.782$); 24 of girls (20.7%) and 14 of boys (16.7%) reported adhering to only regular exercise ($p=0.474$), and 49 subjects to both diet and exercise, of whom 21 (18.1%) were girls and 28 (33.3%) were boys ($p=0.013$). In no metformin group ($n=160$), 112 (70.0%) children lost weight, 41 (36.6%) of them lost weight on

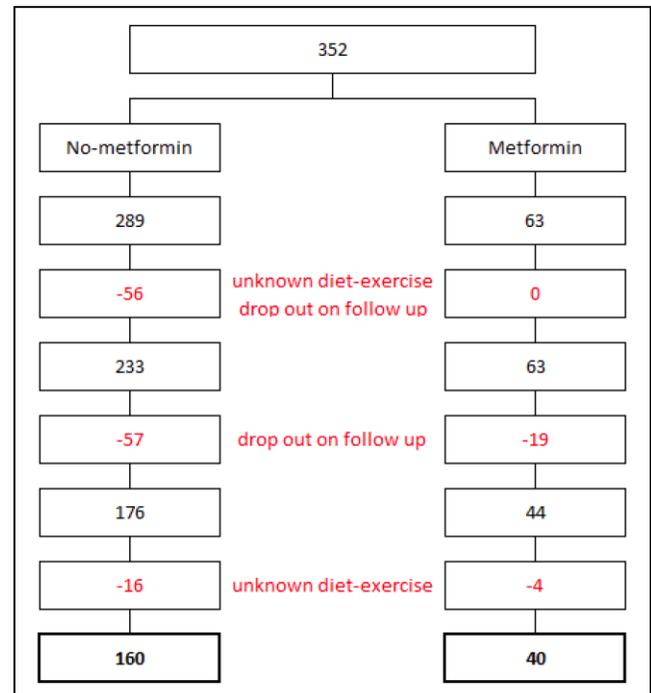


Figure 1: Follow-up diagram.

diet plus exercise, 32 (28.6%) on diet alone and 19 (17.0%) on exercise alone. In the participants who lost weight in the no metformin group, the percentage of reporting adherence to diet were 12.08 times (OR:12.08, 95% CI 3.93-41.66, $p<0.001$). The percentage of regular exercisers only were 3.04 times (OR:3.04, 95% CI 1.18-7.84, $p=0.022$), and the percentage of reporting adherence to both diet and exercise were 32.80 times (OR:32.80, 95% CI 7.14-150.77, $p<0.001$) higher than in those who could not lose weight. The proportion of weight losers was significantly higher in the diet only (88.9%, $p=0.023$) and diet plus exercise (95.3%, $p=0.002$) groups than those just exercising (65.5%). Gender and Tanner stage had no significant effect on weight loss. However, there was no significant difference in the median amount of weight loss between the metformin group and the no metformin group for p to 12 months. During the first-month control, the percent of the patients who lost weight was 77.8% (28/36) in the metformin group and 88.4% (99/112) in the non-metformin group. At the twelfth month, just 13.8% were still on follow-up (Table 2).

DISCUSSION

Obese children and adolescents are at a greater risk of harm to physical health than obese adults due to longer exposure time. Also, they struggle with a range

Table 2: Amount of Maximum Weight Loss in Metformin and no Metformin Groups^{1,2}

	Metformin (-)			Metformin (+)			p
	n	Median [25%-75%]	min-max	n	Median [25%-75%]	min-max	
m1-m0	70	1.73 [0.78-3.01]	0.05-8.30	22	1.30 [0.44-2.76]	0.15-6.60	0.303
m3-m0	26	3.53 [1.06-6.81]	0.25-22.50	8	3.60 [1.20-5.53]	0.50-9.70	0.693
m6-m0	12	3.40 [1.44-5.61]	0.30-6.55	3	4.50 [3.75-8.15]	3.75-8.15	0.101
m12-m0	4	4.54 [3.63-7.76]	3.35-8.80	3	2.80 [1.35-3.55]	1.35-3.55	0.114

¹Maximum lost amount was evaluated for patients who lost weight more than one follows up. There were 160 amounts from 112 weight loss in the no-metformin group and 53 from 36 in the metformin group.

²Amounts of loss were calculated by subtracting the follow-up month's weight from baseline weight. m1-m0 means the difference of patient's weight between 1 month follow up and baseline, m3-m0 the difference of patient's weight between 3 month follow up and baseline, m6-m0 the difference of patient's weight between 6 months follow up and baseline, m12-m0 the difference of patient's weight between 12 months follow up and baseline, respectively.

of psychosocial difficulties, including decreased self-esteem, challenges in peer relationships, and depression [9, 10].

This report describes a specialty clinic's experience of basal and prognostic findings in a relatively large group of obese children to whom a low carbohydrate diet and exercise were recommended. A considerable mass of childhood obesity studies objects ranging from community-based to tertiary care based from observational to placebo-controlled. We use plenty of intervention methods such as psychological, medical, surgical treatments, structured dynamic group studies, and approaches based on innovative techniques such as new devices or software [13-15]. Awaiting the long-term results of the search for the best methodology, our time as the response in the first degree (i.e., pediatric endocrinologists) in the daily practice is running, and generally speaking, we are not aware of outcomes. Therefore, we conducted this observational, partly prospective study to share our clinical experience. Our execution's distinctive characteristics might be the large, heterogeneous background population mainly from rural and suburban communities and a flexible non-calorie-restricted, low carbohydrate diet without prescriptions and calculations. Although BMI normative data are lacking for those younger than age 3, our ten cases aged <3 had considerable high BMI allowing their definition as obese. Thus we recruited them as well. We found a high frequency of biochemical disturbances at first evaluation. As calculated using HOMA-IR, in 57.1% of cases, insulin resistance was

present, reaching even most patients with Tanner stage 5 puberty (86.0%). A study of 220 children aged 5-14 yrs. from Brazil found HOMA-IR above 3.43 in 33.2% of cases [22]. Another study from New York of 362 overweight/obese 7-12 old's found 56.5% was insulin resistant using the cut-off ≥ 2.6 [22]. In the study of 71 children with more comparable cut-offs regarding ours (HOMA-IR prepubertal >2.5 , pubertal >4 body mass index >95 th percentile), insulin resistance was observed in 58% of the cases [24]. To our surprise, similar insulin resistance rates come up when similar cut-offs are used; thus, 56-58% insulin resistance rate could be generalized as one of the metabolic features of childhood obesity.

We detected Type 2 diabetes in a small proportion of our cases (3.1%). Literatur data are ranging between 0.4–13% [25, 26]. Considering the lack of analysis of our OGTT data and data of patients classified as diabetes at first attendance, diabetes prevalence in obese children and adolescents is expected to increase in our population. In a study conducted on 448 obese children in Milan, people with diabetes were much less, with 0.7% [26]. On the other hand, in a broader sense, dysglycemia was detected in 31.4% of our cases.

We analyzed in this cohort dyslipidemia carefully in different aspects using age and sex-matched standards. Following previous data, hypertriglyceridemia was the most frequent finding, followed by low HDL. Also, at least one dyslipidemia finding was detected in nearly half of the subjects [27].

Overall, 81.3% of the cases had at least one abnormality in any of the biochemical parameters. When we analyzed subjects' adherence to treatment recommendations, boys' self-reported adherence was significantly higher for diet and insignificantly for exercise than girls, both still unfavorable. Drop out rate was increased when considering the end of the first year. Regarding the literature findings, compliance is low, and adherence rates vary in childhood obesity treatment [14]. As expected, those reporting adherence lost significantly more weight.

The evidence for the clinical effectiveness of the current weight management program for children remains scarce. Interventions are addressing healthy nutrition and improved levels of physical activity in general. The mean difference in body mass index standard deviation score (BMI z-value) identified in the Cochrane meta-analysis of lifestyle interventions for obesity in children under 18 years old, including behavioral interventions, is -0.04 at the termination of the intervention (12 months) [29]. Community-based interventions seem more effective [29, 30]. However, the Lifestyle Education for Activity Program (LEAP) study found that the intervention did not achieve sustained weight reduction [15]. We did not use BMI Z score change since the reference standards are not continuous data, and weight change is more sensitive for defined periods.

In our study, 151 (55.7%) children had first-degree, obese relatives. There is strong epidemiological evidence that children living in a family with an obese parent are more likely to develop obesity. Thus, an intervention to improve both obese children and parents' weight loss seems a logical strategy to more fully engage a family in fundamental changes to lifestyle behavior [32]. In another study from Turkey, Araz *et al.* found a 27% obesity rate in the siblings of obese children and adolescents [33]. Our family-based approach seems to motivate both the child and other family members to change eating habits. There is consensus that clinicians prescribe and support intensive lifestyle modification controlling caloric intake through portion control, reducing saturated dietary fat intake for children older than two years of age [34]. In our opinion, this approach is optimistic and often fails in daily practice. Many different diets have been proposed for weight loss. There is currently a debate about whether a low-fat (usually 30% of calories as fat) or a low-carbohydrate diet is more efficacious.

The efficacy of low-carbohydrate diets was related to overall caloric restriction rather than carbohydrate intake [35, 36]. This is not valid in our experience since our recommendation is not hypocaloric. The limitation for sugar and starch is balanced with calories from proteins and especially from fat. Thinking on an obese subject in an obese environment, the success of a low-fat, low-calorie diet may depend on a firm intention of the individual and psychosocial support of caregivers and community. Therefore, such attempts mostly end up with disappointment. Decreasing carbohydrates, which causes a concomitant decrease in insulin secretion and ad libitum intake of proteins and fats, eases satiety in every sense and itself. Low insulin leads to more triglyceride lipolysis into free fatty acids and fat loss. The present study demonstrated that a low carbohydrate diet and exercise guide to significant weight loss in obese children despite ad libitum caloric intake. This is consistent with previous investigations describing low carbohydrate diets' effectiveness in promoting weight loss [37-38]. Sondike *et al.* reported a low carbohydrate diet leads to more significant weight loss over a 12 week than a low-fat diet [37]. A Low carbohydrate, moderate-fat, and protein diet is more comfortable for adolescents to follow than a low-fat diet, and a low carbohydrate diet doesn't harm the lipid profile. Siegel *et al.* demonstrated that a low carbohydrate diet is a safe, practical, and effective intervention for obese teens in a pediatrics office setting [38]. Kirk *et al.* reported a low carbohydrate diet reduced glycemic load or standard portion-controlled diets were all effective adiposity measures and clinical outcomes. None of these diets were found to have systemic adverse effects [39].

Physical activity alone is not an effective method for achieving initial weight loss as a first interventional option. However, it is essential for maintaining weight loss achieved through dietary intervention [40]. Our results suggest that both diet only and diet plus exercise were significantly more effective than exercise alone at one year.

The use of metformin in non-diabetic obese people has been demonstrated to cause reduced food intake and weight loss with a reduction in fasting glucose, cholesterol, and insulin concentrations. As depicted in a review article in 2011, 4 out of 6 double-blind placebo-controlled metformin treatment trials in obese children and adolescents revealed significant weight loss in six months [41]. Our results support these findings partly since there was no significant difference

in weight loss between the metformin group and no metformin group. Still, the proportion of the subjects losing weight was higher in the metformin group versus the no metformin group from baseline the 12 months follow-up. We are planning further analysis of our study population through data processing and extension of follow-up to derive more decisive conclusions about the prognosis.

In our study, the frequency of visits varied from weekly to once a year. After one year, we found that 13.8% is still on follow-up. This was the limitation of the study. Noncompliance, dropouts from follow-up is a general problem when dealing with obese subjects. Personal experience is telling that this might mean unsuccess and success concomitantly. Our study is not originating from a strict trial design. One should be empathetic against a schoolchild or a low-income parent escaping hospital visits; in the long term, our observation is these individuals are never lost to follow-up totally; they often show-up after a while. A welcoming and supportive approach and "user-friendly" lifestyle recommendations are favorable, especially in communities with loose socioeconomic backgrounds. Calling back the family is a useful motivator.

In conclusion, obesity in this young age group is severe harm to health, and low carbohydrate lifestyle modification is promising in our experience. Despite the frustrating noncompliance rate among clients, dieting and physical exercise can produce weight loss that can be maintained. Diet is sufficient, but in the long-term follow-up, the polyclinic visits and children's determination for weight loss and treatment compliance is not enough. Metformin can be an option for children with insulin resistance and resistance to adhere to diet or exercise.

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