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Assessment of selected lipid parameters in in children exposed to gestational diabetes (GDM) in utero

Ocena wybranych parametrów gospodarki lipidowej u dzieci urodzonych z ciąży powikłanej cukrzycą ciążową (GDM)

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Abstract
Introduction. The assessment of maternal hyperglycemia during pregnancy and lipid profile in the offspring is recently highlighted. **Aim.** The study was undertaken to assess the selected lipid parameters in children exposed to gestational diabetes (GDM) in utero. **Material and Methods.** 50 children, 7–15 years of age, exposed to GDM were compared with 46 control subjects (7–16 years old). In all participants anthropometric parameters (height, weight, waist and hip circumferences) and values of total cholesterol, LDL-, HDL-cholesterol and triglycerides (TG) were measured. BMI, waist-to-hip ratio (WHR) and TG to HDL-cholesterol ratio were calculated. **Results.** The prevalence of overweight/obesity in the study cohort was 38% and 41% in the control (p=0.19). Higher total cholesterol level (p=0.002) and LDL-cholesterol (p=0.007) were found in the study group. In children exposed to GDM significantly higher values of LDL-cholesterol (p=0.02), triglycerides (p=0.02), TG to HDL-cholesterol ratio (p=0.007) and lower HDL-cholesterol (p=0.02) were observed in overweight/obese children compared to slim participants. In the control group, similar results were not noted. In the study group, a positive correlations of TG to HDL-cholesterol ratio and BMI SDS (R_S=0.47, p=0.0006), WHR (R_S =0.31, p=0.03), SDS of birth weight (R_S =0.47, p=0.0006) were found. **Conclusion.** Children exposed to GDM in utero could have a higher risk of dyslipidemia with its cardiovascular complications. Towards observed worse lipid parameters in children with excessive body mass born from pregnancies with GDM, prevention of overweight and obesity in this group seems to be essential.
Key words
gestational diabetes, obesity, cholesterol, triglyceride, lipids

Streszczenie
Wstęp. Aktualne dane z piśmiennictwa wskazują na związek matczynej hiperglikemii w okresie ciąży z występowaniem zaburzeń lipidowych u potomstwa. **Cel pracy.** Analiza wybranych parametrów gospodarki lipidowej u dzieci pochodzących z ciąży powikłanej cukrzycą ciążową (GDM). **Materiał i metody.** Grupę badaną stanowiło 50 dzieci w wieku 7–15 lat urodzonych z ciąży powikłanej cukrzycą ciążową, grupę kontrolną 46 zdrowych dzieci w wieku 7–16 lat pochodzących z ciąży niepowikłanej GDM. U badanych dokonano pomiaru wysokości i masy ciała, obwodu talii i bioder. Obliczono BMI i wskaźnik talia-biodra (WHR). Z krwi żylnej oznaczono stężenie cholesterolu całkowitego, frakcji LDL-CH, HDL-CH oraz triacylogliceroli (TG). Wyznaczono wartość wskaźnika TG/HDL-CH. **Wyniki.** Nadwagę lub otyłość rozpoznano u 38% dzieci z grupy badanej i 41% z grupy kontrolnej (p=0,19). W grupie badanej wykazano istotnie wyższe stężenie cholesterolu całkowitego (p=0,002) oraz LDL-CH (p=0,007) w porównaniu z grupą kontrolną. Analiza lipidogramu względem BMI w grupie dzieci eksponowanych na GDM wykazała istotnie

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wyższe stężenie LDL-CH (p=0,02), triacylogliceroli (p=0,02), wartość wskaźnika TG/HDL-CH (p=0,007) oraz niższe stężenie HDL-CH (p=0,02) u dzieci z nadwagą i otyłością w porównaniu do dzieci szczuplejszych. Podobnych zależności nie obserwowano w grupie kontrolnej. W grupie badanej stwierdzono korelację wskaźnika TG/HDL z SDS BMI (Rs=0,47, p=0,0006), WHR (Rs=0,31, p=0,03) oraz SDS urodzeniowej masy ciała (Rs=0,47, p=0,0006). **Wnioski.** Dzieci pochodzące z ciąży powikłanej GDM, zwłaszcza z nadwagą lub otyłością, mogą mieć zwiększone ryzyko występowania zaburzeń lipidowych oraz wynikających z nich powikłań sercowo-naczyniowych. W związku z tym szczególnie istotne jest zapobieganie rozwojowi nadmiernej masy ciała w tej grupie dzieci.
Słowa kluczowe
cukrzyca ciążowa, otyłość, cholesterol, triglicerydy, lipidy

Introduction

Many studies show the relationship of the intrauterine development and the risk of chronic diseases. There is a growing amount of evidence that an abnormal fetal growth is related to an increased risk of future health problems such as cardiovascular diseases (hypertension, coronary heart disease) or metabolic complications (hyperlipidemia, hypercortisolemia, obesity, glucose intolerance, insulin resistance, type 2 diabetes mellitus) [1,2].

In recent years, the prevalence of gestational diabetes is constantly increasing [3]. The diabetic intrauterine milieu has a great impact on a developing fetus. Fetal programming caused by GDM may have a long-lasting effect and predispose to obesity and its consequences [4,5]. The epidemiological studies of children exposed to maternal diabetes in utero showed the correlation of increased birth weight with the occurrence of overweight and obesity in the future, in contrast to unexposed children with increased birth weight [6]. Fetal exposure to diabetes or maternal obesity is also associated with an increased risk and progression of atherosclerosis [7]. To date, there are very few publications available that assess the lipid profile in children born from pregnancies with GDM. Due to the fact that primary prevention of atherosclerosis should be implemented early, it is essential to identify if children born from pregnancies with gestational diabetes are at high-risk.

Aim

The aim of this study was to assess the selected lipid parameters, as one of the risk factors for atherosclerosis, in children exposed to gestational diabetes mellitus in utero.

Materials and Methods

The research was approved by the Bioethics Committee of Pomeranian Medical University in Szczecin and written consent of the patients and their parents was obtained. The study was conducted in a cohort of 96 children. The study group consisted of 50 patients, 7–15 years of age (mean 10.8±2.1), 22 girls (44%) and 28 boys (56%), exposed to gestational diabetes mellitus in utero. The control group comprised 46 healthy children, randomly invited to the study by announcements in family practices, 7–16 years of age

Table I. Anthropometric characteristic of study participants
Tabela I. *Parametry antropometryczne w grupie badanej i kontrolnej*

Feature Cecha	Study group (n=50) Grupa badana (n=50)		Control group (n=46) Grupa kontrolna (n=46)		p
	Mean ± SD Średnia ± SD	Median Mediana (min. – max.)	Mean ± SD Średnia ± SD	Median Mediana (min. – max.)	
Height SDS SDS wysokości ciała	0.28±1.11	0.28 (-1.84±2.02)	0.81±1.03	0.73 (-1.49±3.64)	0.02
Weight SDS SDS masy ciała	1.36±2.28	1.03 (-2.35±6.88)	1.67±1.94	1.66 (-2.35±6.05)	NS
BMI SDS SDS BMI	1.53±2.48	1.22 (-2.59±7.02)	1.48±2.11	1.02 (-2±6)	NS
Waist circumference SDS SDS obwodu talii	2.29±2.52	1.72 (-2±7.13)	1.93±2.02	1.54 (-1.55±6.15)	NS
Hip circumference SDS SDS obwodu bioder	0.86±1.81	0.60 (-3.01±4.84)	0.88 ± 1.56	0.92 (-2.54±4.18)	NS
Waist-to-hip ratio Wskaźnik talia-biodra	0.89±0.06	0.89 (0.77-1.04)	0.86±0.06	0.86 (0.72-1.02)	NS

(mean 10.8±3.0), 21 girls (45.7%) and 25 boys (54.3%) from non-diabetic pregnancies. The participants were admitted to the Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age of the Pomeranian Medical University of Szczecin, Poland. Data including the course of pregnancy (also GDM treatment), anthropometric parameters and status of a newborn, dietary habits in the first year of life and family history for diabetes mellitus were obtained from the interview and medical records. Pediatric physical examination with Tanner assessment of pubertal development was conducted. In all children height, weight, waist and hip circumferences were measured. Body mass index (BMI), waist-to-hip ratio (WHR) were calculated. The overweight/obesity was diagnosed if child's BMI was at 85th percentile or higher. The anthropometric characteristic of the participants is presented in Table I. In all children values of total cholesterol, LDL-, HDL-cholesterol and triglycerides were measured. The ratio of TG to HDL-cholesterol was determined.

Statistical methods

The Mann-Whitney test was used to compare measurable variables between the groups. Correlations between measurable variables within each group were analyzed by Spearman's rank correlation coefficient (Rs). The threshold p value for statistical significance was set at $p<0.05$. The analysis was performed using the Statistica 10.

Results

The prevalence of overweight/obesity in the study group was 38%, in the control group 41% (p=0.19). In all subjects values of total cholesterol, LDL-, HDL-cholesterol and triglycerides were measured. The ratio of TG to HDL-cholesterol was determined.

Children exposed to GDM had significantly higher concentrations of total cholesterol (p=0.002) and LDL-cholesterol (p=0.007) in comparision to the control group (Tab. II).

The relationship of chosen lipid and anthropometric parameters was analyzed. In participants from diabetic pregnancies with excessive weight, comparing to slim children of diabetic mothers, higher LDL-cholesterol (p=0.02), triglicerydes (p=0.02) and lower HDL-cholesterol (p=0.02) levels were noted (Tab. III). In the study group, higher TG to HDL-cholesterol ratio was observed in children with overweight/obesity compared to slim children (p=0.007, Fig. 1). Similar relationship in the control group was not found (Fig. 2). In children exposed to gestational diabetes in utero, in contrast to the control, a correlations of TG to HDL-cholesterol ratio and BMI SDS (Rs=0.47, p=0.0006; Fig. 3), waist-to-hip ratio (Rs=0.31, p=0.03; Fig. 4) and SDS of birth weight (Rs=0.47, p=0.0006; Fig. 5) were noted.

Discussion

The increasing incidence of GDM, as a consequence of the introduction of International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria, is currently widely discussed [8,9]. More cases of GDM will cause the increase in the number of children exposed to gestational diabetes in utero. Many studies show a higher risk of obesity in offspring of mothers with gestational diabetes [10,11], however the direct relationship has not been confirmed. In our investigation

Table II. Lipid parameters of study participants

Tabela II. *Parametry gospodarki lipidowej w grupie badanej i kontrolnej*

Feature Cecha	Study group (n=50) Grupa badana (n=50)		Control group (n=46) Grupa kontrolna (n=46)		p
	Mean ± SD Średnia ± SD	Median Mediana (min.–max.)	Mean ± SD Średnia ± SD	Median Mediana (min.–max.)	
Total cholesterol Cholesterol całkowity [mg/dL]	166.4±26.1	167.5 (123.0–240.0)	147.4±31.8	144.0 (84.0–225.0)	0.002
LDL-cholesterol Cholesterol LDL [mg/dL]	96.4±24.1	98.0 (58.0–180.0)	82.2±27.9	83.0 (31.0–154.0)	0.007
HDL-cholesterol Cholesterol HDL [mg/dL]	60.7±15.9	59.5 (35.0–115.0)	54.5±13.2	52.5 (29.0–97.0)	NS
Triglycerides Triacyloglicerole [mg/dL]	71.4±32.6	62.0 (27.0–180.0)	77.9±31.6	70.0 (37.0–175.0)	NS
TG/HDL-CH ratio Wskaźnik TG/HDL	1.4±0.9	1.0 (0.4–5.0)	1.6±0.8	1.4 (0.4–4.1)	NS

Table III. Lipid parameters of study participants regarding BMI

Tabela III. *Parametry gospodarki lipidowej w grupie badanej i kontrolnej w zależności od BMI*

Feature Cecha	BMI <85th percentile BMI <85. centyla		BMI ≥85th percentile BMI ≥85. centyla		p
	Mean ± SD Średnia ± SD	Median Mediana (min.–max.)	Mean ± SD Średnia ± SD	Median Mediana (min.–max.)	
	STUDY GROUP/GRUPA BADANA				
	n=31		n=19		
Total cholesterol Cholesterol całkowity [mg/dL]	161.4±20.4	168.0 (127.0–206.0)	174.6±32.4	167.0 (123.0–240.0)	NS
LDL-cholesterol Cholesterol LDL [mg/dL]	89.1±17.5	94.0 (58.0–123.0)	108.5±28.6	100.0 (63.0–180.0)	0.02
HDL-cholesterol Cholesterol HDL [mg/dL]	64.9±16.2	63.0 (41.0–115.0)	53.8±23.0	51.0 (35.0–80.0)	0.02
Triglicerydes Triacyloglicerole [mg/dL]	63.1±27.1	54.0 (27.0–129.0)	85.1±36.9	81.0 (39.0–180.0)	0.02
	CONTROL GROUP/GRUPA KONTROLNA				
	n=27		n=19		
Total cholesterol Cholesterol całkowity [mg/dL]	142.8±33.4	141.0 (84.0–225.0)	153.9±29.1	150.0 (107.0–214.0)	NS
LDL-cholesterol Cholesterol LDL [mg/dL]	75.9±29.1	71.0 (31.0–154.0)	91.2±24.3	84.0 (56.0–149.0)	NS
HDL-cholesterol Cholesterol HDL [mg/dL]	55.9±13.7	54.0 (29.0–97.0)	52.4±12.6	50.0 (31.0–77.0)	NS
Triglycerides Triacyloglicerole [mg/dL]	80.2±36.8	65.0 (37.0–175.0)	74.7±22.6	77.0 (44.0–132.0)	NS

the prevalence of overweight/obesity in the study group was 38%, in the control 41% and the difference was not significant. Similarly, Donovan et al. highlights the lack of direct relationship between exposition to GDM in utero and the risk of overweight/obesity in the future [12]. No differences in the percentage of overweight/obesity between study and control group may be the result of effective screening of GDM and appropriate, intensive treatment thanks to the approved diagnostic criteria. That improves the mother's glycemic control and intrauterine environment for growing fetus, decreasing the risk of i.e. macrosomia and its future consequences. Additionally, the increasing incidence of overweight/obesity in general pediatric population may be responsible for a high percentage of children with excessive body weight in the control group and mask the effect of maternal diabetes.

However, Chandler-Laney et al. [13] showed that offspring of mothers with GDM have greater trunk fat and when gain weight, they preferentially deposit fat in the abdomen. The underlying mechanism may be hyperinsulinemia found in these children [14–16]. These findings suggest that exposure to gestational diabetes in utero, especially combined with overweight status, may worsen child's metabolic profile.

In the presented study, except of the lipid parameters, we calculated the triglycerides to HDL-cholesterol ratio. This indicator is used as one of predictors of atherosclerosis and cardiovascular risk [17, 18].

In the study group an adversed lipid profile was observed, with significantly higher concentrations of total cholesterol and LDL-cholesterol in comparision to the control cohort. Moreover, in children exposed to GDM, the coexsistence of excessive body weight "worsened" the lipid parameters. In

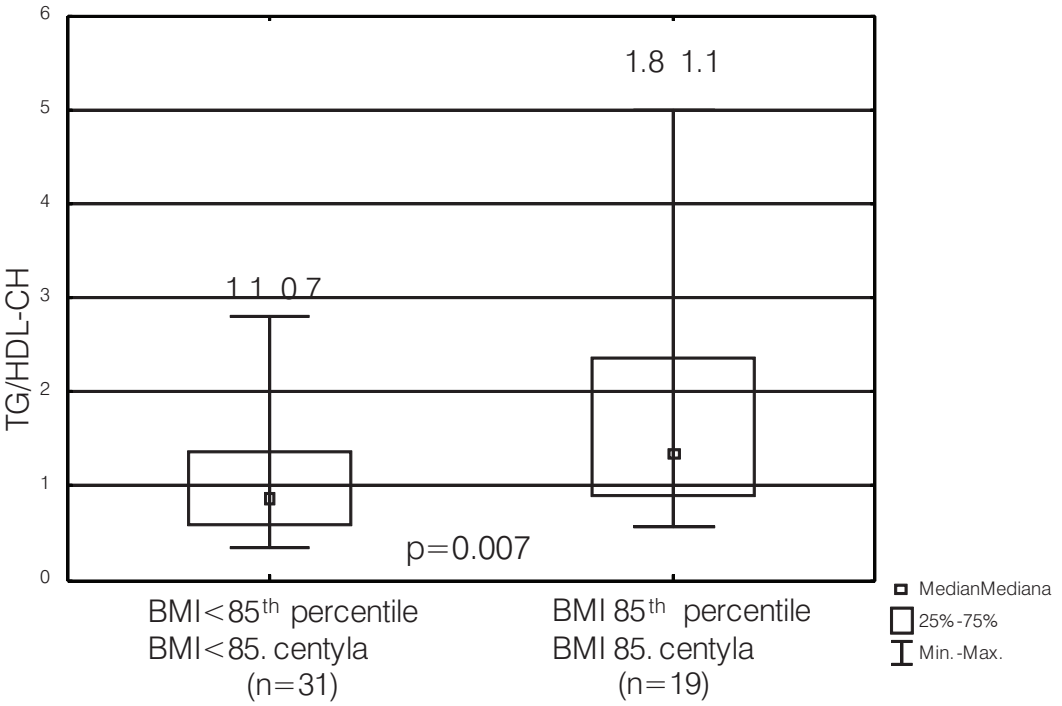

Fig. 1. TG to HDL-cholesterol ratio (TG/HDL-CH) regarding BMI in the study group
Ryc. 1. *Wskaźnik TG/HDL w zależności od BMI w grupie badanej*

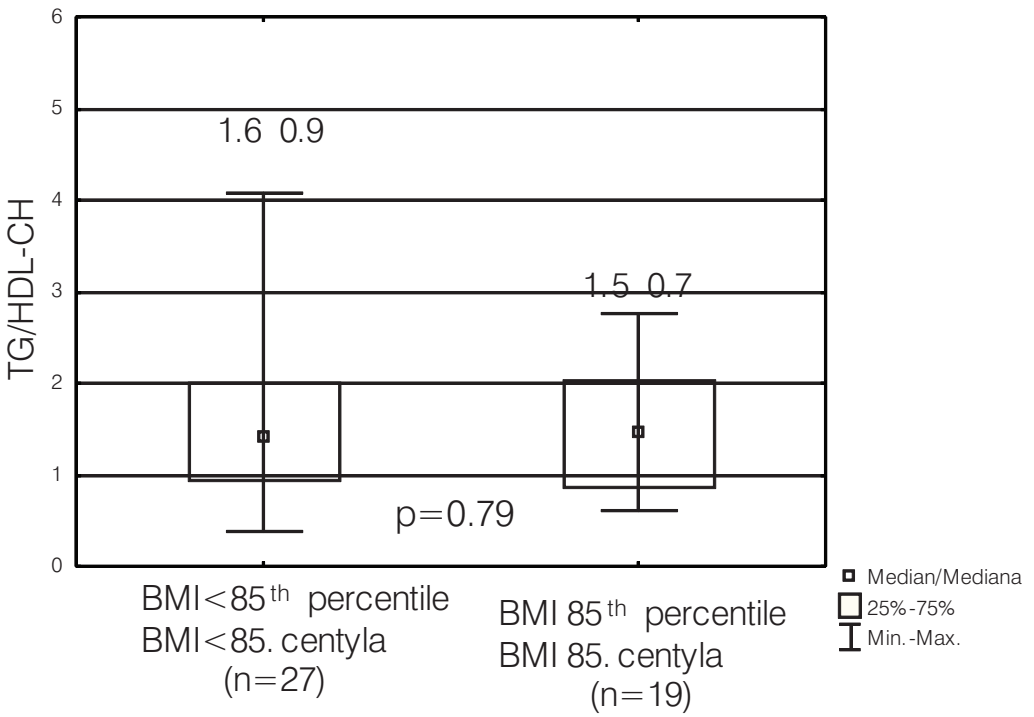

Fig. 2. TG to HDL-cholesterol ratio (TG/HDL-CH) regarding BMI in the control group
Ryc. 2. *Wskaźnik TG/HDL w zależności od BMI w grupie kontrolnej*

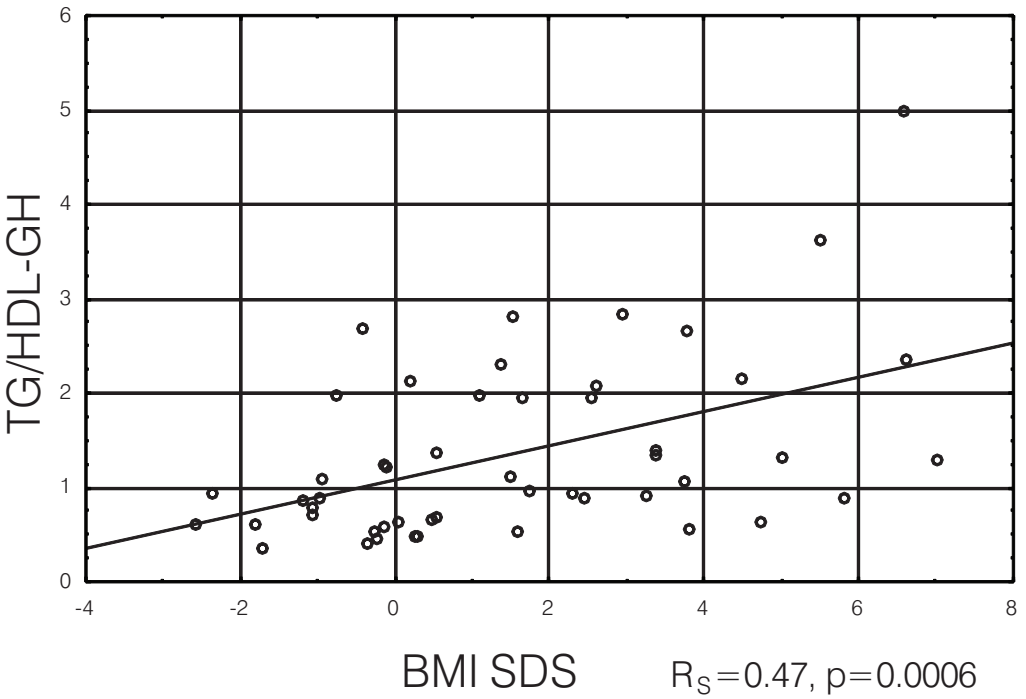

Fig. 3. Correlation of TG to HDL-cholesterol ratio (TG/HDL-CH) and BMI SDS in the study group
Ryc. 3. *Związek wskaźnika TG/HDL z SDS BMI u dzieci z grupy badanej*

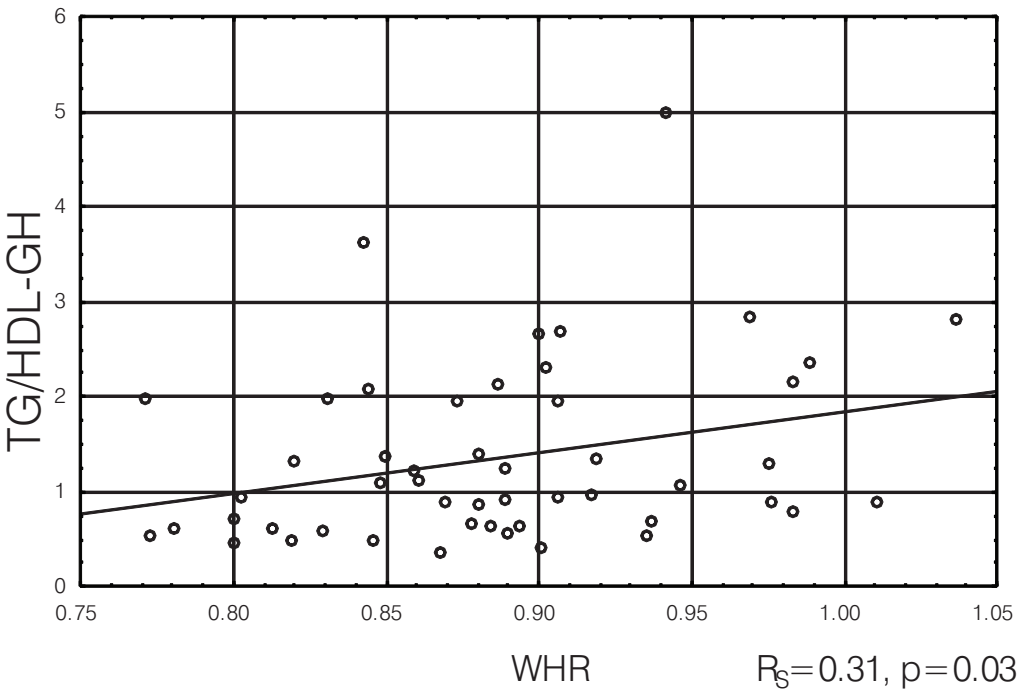

Fig. 4. Correlation of TG to HDL-cholesterol ratio (TG/HDL-CH) and waist-to hip ratio (WHR) in the study group
Ryc. 4. *Związek wskaźnika TG/HDL ze wskaźnikiem talia-biodra (WHR) u dzieci z grupy badanej*

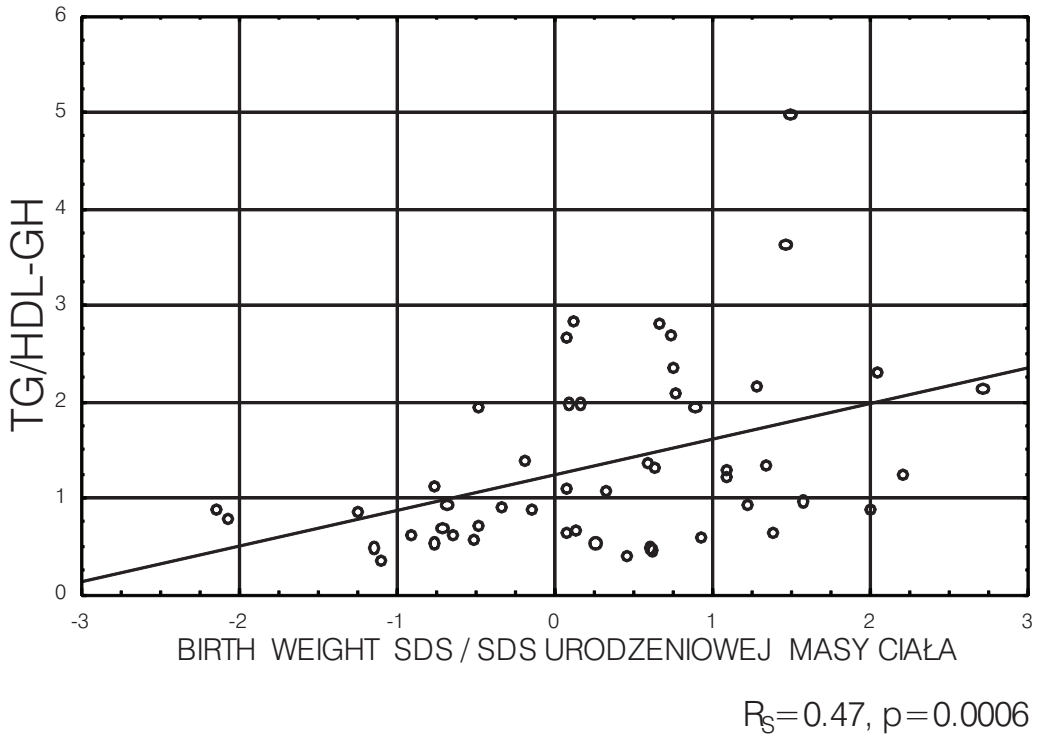

Fig. 5. Correlation of TG to HDL-cholesterol ratio (TG/HDL-CH) and SDS of birth weight in the study group
Ryc. 5. *Związek wskaźnika TG/HDL z SDS urodzeniowej masy ciała u dzieci z grupy badanej*

the study group, in overweight/obese children, conversely to the slim participants, significantly lower HDL-cholesterol and higher values of LDL-cholesterol, triglycerides and TG to HDL-cholesterol ratio were observed. A similar relationship was not found in the control group. We also noted that the higher anthropometric parameters such as: BMI SDS and WHR, the higher cardiovascular risk (expressed in TG to HDL-cholesterol ratio) is observed among children exposed to GDM, as opposite to unexposed group.

To our knowledge, the lipid metabolism in children exposed to gestational diabetes has not been extensively investigated and only few studies have reported their lipid profile. Beyerlein et al., in the group of 12.000 children, did not confirm the relationship of mother's gestational diabetes mellitus and total cholesterol concentration in offspring (in this study full lipid profile was not assessed) [19]. However, Manderson et. al pointed the adversed lipid profile (higher total and LDL-cholesterol concentrations) in children born from GDM pregnancies, compared to their peers from uncomplicated pregnancies [20]. Our results are consistent with the observation that children born from pregnancies with GDM present higher triglyceride concentrations and lower HDL-cholesterol [13]. This pattern of dyslipidemia might also be secondary to hyperinsulinemia, which has been confirmed in previous studies [21, 22]. The mechanism of this phenomenon is complex and may involve the inhibition of HDL-cholesterol biosynthesis by direct effect of insulin [23]. It may also include the effect of decreased insulin sensitivity that increases hepatic synthesis of very low density lipoprotein triglycerides, leading to lipoprotein remodeling which presents as low HDL-cholesterol concentrations [24, 25]. Consequently, children exposed to GDM during pregnancy may be predisposed to develop metabolic complications of this state.

In our study the unique observation is the association of birth weight and the risk of atherosclerosis (expressed in TG to HDL-cholesterol ratio) in children born to GDM mothers. Previous studies highlight mainly the relationship of cardiovascular risk and anthropometric parameters at birth as a consequence of a higher prevalence of obesity in children born with higher birth weight, independently of lipid profile [26]. There are also studies reporting normal lipid profile in children unexposed to GDM but born with macrosomia [27]. Therefore, our results suggest that intrauterine exposure to diabetic milieu and abnormal fetal growth, irrespective of current weight status, may predispose to cardiovascular complications in future.

The strength of the study was the detailed analysis of anthropometric parameters, including those at birth and dichotomy of children into normal weight and overweight groups which enabled the effect of the exposure to GDM in utero to be evaluated independently of child's weight status. This study was limited by the small sample size and lack of detailed information regarding maternal glycemic control during pregnancy.

Available data concerning lipid profile and the risk of atherosclerosis and its complications in children born from pregnancies with gestational diabetes are still very limited. The results of our study suggest that this group of children may have higher risk of cardiovascular diseases in future. However, further and detailed studies should be done to fully confirm that observation.

Conclusion

Children exposed to gestational diabetes in utero, in spite of similar prevalence of overweight/obesity compared to their non-exposed peers, could have a higher risk of dyslipidemia and atherosclerosis with its cardiovascular complications. Towards observed worse lipid parameters in children with excessive body mass born from pregnancies with GDM, prevention of overweight and obesity in this group seems to be essential.

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