Endokrynologia Polska
DOI: 10.5603/EP.2014.0047
Tom/Volume 65; Numer/Number 5/2014
ISSN 0423–104X

Serum resistin concentrations in children with type 1 diabetes mellitus — negative relation to body fat mass

Stężenie rezystyny w surowicy u dzieci z cukrzycą typu 1 — negatywna relacja z masą tłuszczową ciała

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Abstract

Introduction: Insulin is one of the major factors regulating adipose tissue function. On the other hand, adipocytes secrete adipocytokines that may influence insulin synthesis and action, and are involved in blood glucose regulation. In type 1 diabetes mellitus (t1DM), beta cells function is replaced with exogenous insulin therapy. This raises a question concerning the impact of t1DM on adipose tissue secretory function. The aim of this study was to evaluate one of the adipocytokines, resistin, serum concentrations in relation to body fat mass in children with t1DM.

Material and methods: The study comprised 75 children with t1DM and a control group of 20 healthy coevals. All children had estimated serum resistin concentrations, glycated haemoglobin levels, growth and body weight measurements, and bioelectrical impedance analysis in order to establish body composition.

Results: Resistin serum concentrations were significantly lower in children with t1DM vs. controls (median values: 343 *vs.* 590 pg/mL; mean values ± SD: 577 ± 561 *vs.* 861 ± 628 pg/mL; $p < 0.001$), and they negatively correlated with body fat mass ($p = 0.022$) and age ($p = 0.022$) in the t1DM group, but not in the control group. Disease duration, glycated haemoglobin levels and insulin dosage revealed no direct statistical relation to resistin levels.

Conclusions: Diminished serum resistin concentrations and a negative correlation between resistin levels and body fat mass in children with type 1 diabetes seem to result from broken physiological adipo-insular regulations, independent of disease duration, its metabolic control and insulin supply. **(Endokrynol Pol 2014; 65 (5):342–347)**

Key words: *resistin; type 1 diabetes; adipose tissue; insulin; children*

Streszczenie

Wstęp: Insulina jest jednym z głównych czynników regulujących funkcje tkanki tłuszczowej. Z drugiej strony, adipocyty wydzielają adipocytokiny, które mogą wpływać na sekrecję i działanie insuliny oraz brać udział w regulacji stężenia glukozy we krwi. W cukrzycy typu 1 sekrecja insuliny przez komórki beta zostaje zastąpiona przez egzogenną insulinoterapię. Powstaje pytanie o wpływ tej choroby na czynność sekrecyjną tkanki tłuszczowej. Celem pracy była ocena stężenia jednej z adipocytokin, rezystyny, w surowicy dzieci z cukrzycą typu 1, oraz związku oznaczonej rezystynemii z masą tkanki tłuszczowej.

Materiał i metody: Badaniami objęto 75 dzieci z cukrzycą typu 1, oraz grupę kontrolną 20 zdrowych dzieci. U wszystkich wykonano oznaczenia stężenia rezystyny w surowicy, poziomu hemoglobiny glikowanej, pomiary wzrostu i masy ciała, oraz badanie impedancji bioelektrycznej celem oceny składu ciała.

Wyniki: Stężenia rezystyny w surowicy były niższe u dzieci z cukrzycą typu 1 niż w grupie kontrolnej (mediana: 343 *vs.* 590 pg/ml, średnia ± SD: 577 ± 561 *vs.* 861 ± 628 pg/ml, $p < 0{,}001$) oraz korelowały ujemnie z masą tkanki tłuszczowej ($p = 0{,}022$) oraz wiekiem ($p = 0{,}022$) w grupie dzieci z cukrzycą, ale nie w grupie kontrolnej. Czas trwania choroby, poziom hemoglobiny glikowanej i dawkowanie insuliny nie wykazały bezpośredniego związku statystycznego ze stężeniami rezystyny.

Wnioski: Obniżone stężenie rezystyny w surowicy oraz ujemna korelacja między stężeniami rezystyny i masą tłuszczową ciała u dzieci z cukrzycą typu 1 wydają się wynikać z przerwania fizjologicznych regulacji adipo-insularnych, niezależnie od czasu trwania choroby, jej kontroli metabolicznej i podaży insuliny. **(Endokrynol Pol 2014; 65 (5): 342–347)**

Słowa kluczowe: *rezystyna; cukrzyca typu 1; tkanka tłuszczowa; insulina; dzieci*

Introduction

Glucose plasma concentration under physiological conditions is maintained at a relatively constant level, despite the fact that carbohydrates are not continuously supplied in the diet. Maintaining such a state requires the consistent co-operation of several mechanisms.

One of the main roles is played by the beta cells of pancreatic islets. In the abundance of energy substrates, they secrete insulin, which enables efficient

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cellular glucose uptake, as well as its metabolism, or deposition as a reserve. On the other hand, when energetic substrates are deficient in the diet, low concentrations of insulin promote hepatic gluconeogenesis and glycogenolysis, as well as lipolysis in adipose tissue [1–3]. However, adipose tissue is not only a reservoir for energy excess, but also an endocrine organ. A number of biologically active substances it produces — adipocytokines — can both prevent hyperglycaemia (such as leptin, adiponectin) and promote it (TNF-α, most other cytokines) [4–8]. The importance of adipose tissue for carbohydrate management is confirmed by clinical observations — both its excess (obesity) and deficiency (including lipodystrophy) are associated with insulin resistance and a tendency to elevated glucose levels [1, 9].

One of the adipocytokines is resistin — a protein hormone that seems to be involved in the process of blood glucose regulation, although its biological function in humans has not been fully identified yet [10, 11].

Studies carried out on rodent models have demonstrated that resistin intensifies gluconeogenesis and glycogenolysis — increasing hepatic insulin resistance and elevating blood glucose levels. Chronic hyperresistinaemia observed in rats leads to a systemic insulin resistance, involving skeletal muscles and adipose tissue, and it results in glucose intolerance, hyperinsulinaemia and hypertriglyceridaemia [1, 4, 12–15]. The physiological role of resistin may be maintaining blood glucose level during nutritional deficiencies, while its pathological effects seem to be associated with worsening of glucose utilisation in a state of body fat excess. Resistin concentrations increase in diet-induced obesity and in biological models of genetically determined obesity as well [13, 16].

On the other hand, suppression of resistin activity in rodents exacerbates adipogenesis and causes a consequent increase in adipose tissue mass, along with an enhancement in insulin sensitivity and glucose use [17].

In type 1 diabetes, a number of biological processes responsible for the regulation of blood glucose level are impaired as a result of the absence of endogenously produced insulin — its physiological function is replaced by the exogenous supply, which is not regulated naturally. This raises a number of questions concerning the impact of type 1 diabetes on adipose tissue secretory function. Its disorders may, among others, increase the already increased risk of premature atherosclerosis in children and adolescents with type 1 diabetes [18, 19].

The aim of this study was to establish resistin serum concentrations, and its relation to body fat mass, in children with type 1 diabetes mellitus.

Table I. *Clinical characteristics of patients with type 1 diabetes (N = 75)*

Tabela I. *Charakterystyka kliniczna grupy pacjentów z cukrzycą typu 1 (N = 75)*

	Mean ± SD
Age (years)	12.5 ± 3.5
Diabetes duration (years)	4.9 ± 3.1
HbA1c (%)	7.7 ± 1.4
INS/day [units/day]	42.2 ± 21.1
INS/kg [units/kg]	0.85 ± 0.28

HbA1c — glycated haemoglobin; INS/day — daily insulin dose; INS/kg — daily insulin dose per kg of body weight

Material and methods

The study included 75 children with type 1 diabetes: 30 boys and 45 girls aged four to 17 years with disease duration from one to 15 years (Table I). The patients were in generally good condition, with no acute or chronic complications of diabetes or additional diseases. In the studied group, 35 patients were treated with intensive functional insulin therapy, 21 with continuous subcutaneous insulin infusion, and 19 with the conventional method.

The control group included 20 healthy children: ten boys and ten girls, aged six to 16 years (mean value ± SD: 12.5 ± 2.7).

The following investigations were performed in all children at basic conditions — in the morning, fasting, after a night's rest:

— blood sample obtained to determine resistin serum concentrations and glycated haemoglobin (HbA_{1c}) levels;
— growth and body weight measurements (accurate to 0.1 cm and 0.1 kg, respectively);
— bioelectrical impedance analysis (BIA) in order to evaluate body composition (Akern analyser BIA-101, Bioresearch, the tetrapolar system [20]).

Serum resistin concentration was determined with the radioimmunoassay method (Resistin (43–65) (Human) RIA Kit, Phoenix Pharmaceuticals).

Values of glycated haemoglobin (HbA1c) were obtained with high-performance liquid chromatography — HPLC (Bio-Rad).

The statistical study quantitative traits have been characterised by applying the mean value and standard deviation (SD). Kolmogorov-Smirnov test was used in evaluating the compatibility of the variables with the normal distribution. For the variables not compatible with the normal distribution, nonparametric methods were used: Mann-Whitney test to determine differences in quantitative traits between the two groups, and the Spearman correlation r, in order to assess the coincidence between two quantitative traits. For normally distributed

variables, parametric methods were used: Levene's test of homoscedasticity and t-test to assess the equality of average differences between groups, and Pearson correlations to determine the relationship between two quantitative traits. Statistical study was performed in SPSS for Windows 14.0.

The study protocol was approved by the local Ethics Committee of the Karol Marcinkowski University of Medical Sciences in Poznań. Legal guardians of all participants gave informed consent.

Results

Fat mass analysis

Fat mass values determined with bioelectrical impedance analysis revealed no statistically significant differences between the groups. A comparative statement of the elements of body composition of children with diabetes and their healthy coevals is presented in Table II.

In both the studied and the control group, the amount of fat mass differed depending on the sex: both its total value (FM) and percentage value (compared to the total body weight) of the body fat mass (FM%) was significantly higher in girls than in boys with diabetes (for both features: $p < 0.001$). In the control group, a statistically significant difference was only presented by the parameter FM% ($p = 0.009$), while for the FM no statistical significance was achieved ($p = 0.282$) in spite of the observed tendency for slightly higher values in females.

In the group of children with diabetes, statistical analysis showed a significant, direct dependency of total body fat mass on age and duration of disease, while its value of interest (FM%) did not show a similar dependency.

In the control group, no statistically significant relation between age and either FM ($p = 0.415$) or FM% ($p = 0.072$) was demonstrated.

Glycated haemoglobin, as a parameter of metabolic control in diabetic patients, showed no statistical association with body fat mass.

Table II. *Body mass and its components in children with type 1 diabetes and the control group, as assessed by bioelectrical impedance*

Tabela II. *Masa ciała oraz jej składniki u dzieci z cukrzycą i zdrowych, oznaczone metodą impedancji bioelektrycznej*

	Type 1 diabetes (N = 75)	Control group (N = 20)	P value
	mean ± SD	mean ± SD	
BW [kg]	47.7 ± 15.2	45.8 ± 10.3	> 0.05
MM [kg]	21.8 ± 7.7	22.0 ± 6.8	> 0.05
MM% (%)	45.5 ± 5.9	47.5 ± 5.7	> 0.05
FM [kg]	11.6 ± 5.8	10.5 ± 3.7	> 0.05
FM% (%)	24.5 ± 8.0	23.4 ± 7.1	> 0.05
FFM [kg]	36.1 ± 12.3	35.3 ± 9.3	> 0.05
FFM% (%)	75.5 ± 8.0	76.6 ± 7.1	> 0.05

BW — body weight; MM — total body muscle mass; MM% — percentage value of the body muscle mass; FM — total body fat mass; FM% — percentage value of the body fat mass; FFM — total body fat free mass; FFM% — percentage value of the body fat free mass. No statistically significant differences between the groups

A statistically significant correlation was found in the case of insulin doses used in the treatment — a total daily insulin dose (INS/day) and the calculated dose per kilogram of body weight (INS/kg) showed a direct relationship with the total fat mass, but no relationship with the percentage amount of body fat. The used method of insulin therapy did not show a statistical relationship between body fat mass of children and adolescents and type 1 diabetes. Correlations of body fat mass (FM and FM%) with the clinical data of patients with type 1 diabetes mellitus are presented in Table III.

Resistin concentration analysis

Statistical analysis demonstrated a significant difference in the resistinaemia between the patients and the control group ($p < 0.001$). Children with diabetes had lower re-

Table III. *Correlations of total body fat mass (FM) and its percentage value (FM%) with the clinical data of patients with type 1 diabetes mellitus*

Tabela III. *Korelacje całkowitej masy tłuszczowej ciała (FM) oraz jej wartości procentowej (FM%) z danymi klinicznymi u dzieci z cukrzycą typu 1*

	FM [kg]		FM% (%)	
	R	P value	R	P value
Age (years)	0.491	< 0.001	–0.157	0.179
Diabetes duration (years)	0.330	0.004	0.076	0.518
HbA1c (%)	0.089	0.449	0.068	0.565
INS/day [units/day]	0.541	< 0.001	0.001	0.994
INS/kg [units/kg]	0.238	0.039	0.019	0.874

HbA_{1c} — glycated haemoglobin; INS/day — daily insulin dose; INS/kg — daily insulin dose per kg of body weight.

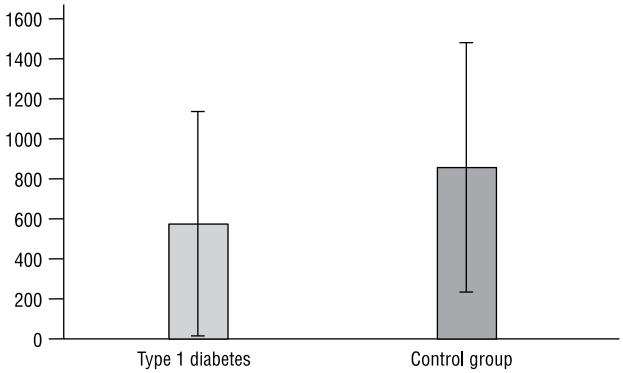

Figure 1. *Mean values of resistin serum concentrations [pg/ml] in children with type 1 diabetes and the control group*

Rycina 1. *Średnie stężenia rezystyny w surowicy [pg/ml] u dzieci z cukrzycą typu 1 i w grupie kontrolnej*

sistin concentrations than their healthy coevals (median value: 343 *vs.* 590 pg/mL, and mean values ± SD: 577 ± 561 pg/mL *vs.* 861 ± 628 pg/mL respectively) (Figs. 1–3).

The assessment of the resistin concentrations dependence on body composition in children with diabetes showed a negative correlation with the total fat mass (FM) as determined with bioelectrical impedance, with no relation to the percentage value (FM%), or the total body weight. None of these correlations was observed in the control group.

In neither of the groups, namely patients with diabetes and healthy children in the control group, were statistically significant gender-related differences in resistinaemia found.

The resistin concentrations observed in the diabetic group presented a statistically significant, inversely proportional dependence on age — along with the advancement of age the resistinaemia value decreased. Such dependence was not observed in the control group.

Neither the duration of diabetes nor its metabolic control, measured as the glycated haemoglobin value, showed statistically significant dependence on the concentrations of resistin. The evaluation of the relationship between resistinaemia and the individual daily dose of insulin in patients with diabetes showed no correlation with any of the applicable conversion methods (INS/day, INS/kg). Resistin concentrations showed no dependence on the method of insulin therapy.

Correlations of serum resistin concentrations with clinical data are presented in Table IV.

Discussion

Despite studies showing a significant role of resistin in the development of insulin resistance in rodents, its role in humans is still not fully understood. Research projects carried out with different groups of patients have tried to answer questions about the role of resistin in, among others, the pathogenesis of insulin resistance, inflammation and related diseases [4]. Also, the impact of type 1 diabetes mellitus on resistin secretion remains unclear.

Fehman et al., comparing resistin concentrations in patients with type 1 diabetes, type 2 diabetes and healthy individuals, found similar levels in all subjects [21]. On the other hand, Schäffler et al., in a large study of 555 adult patients with type 2 diabetes, 114 patients with type 1 diabetes, and 216 healthy subjects, reported significantly higher resistin concentrations in healthy

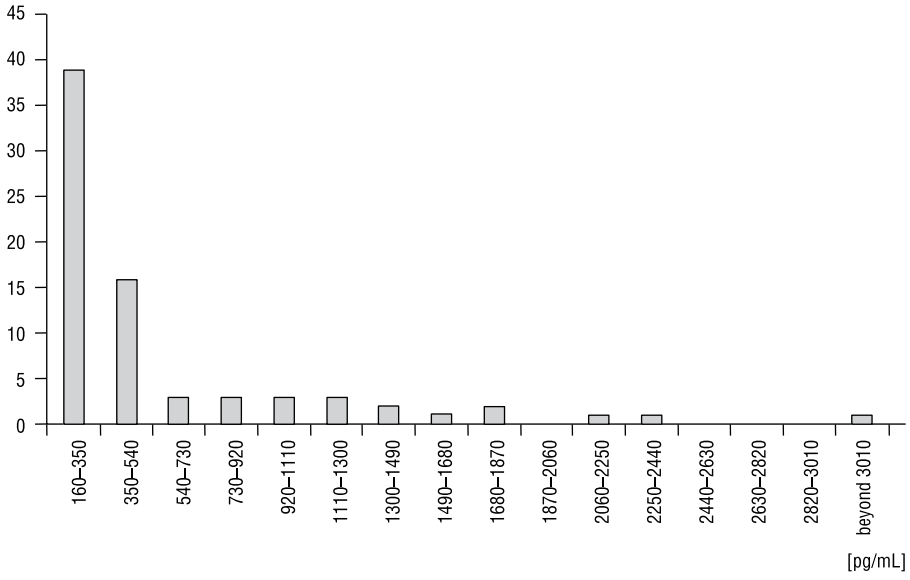

Figure 2. *Histograms for resistin serum concentrations in children with type 1 diabetes (N = 75)*

Rycina 2. *Histogramy dla stężeń rezystyny w surowicy w grupie dzieci z cukrzycą typu 1 (N = 75)*

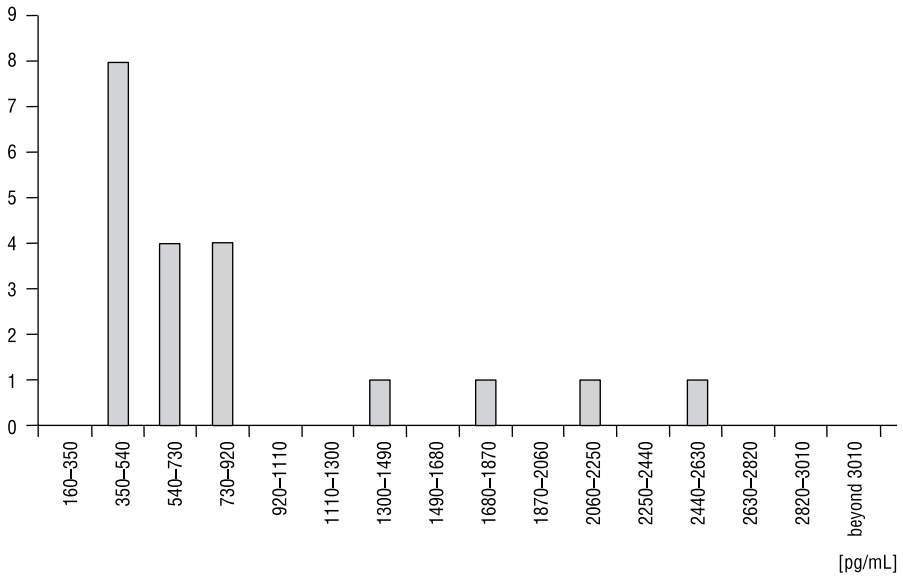

Figure 3. *Histograms for resistin serum concentrations in control group (N = 20)*
Rycina 3. *Histogramy dla stężeń rezystyny w surowicy w grupie kontrolnej (N = 20)*

Table IV. ***Correlations of serum resistin concentrations with clinical data among analysed groups***
Tabela IV. ***Korelacje stężeń rezystyny w surowicy z danymi klinicznymi w analizowanych grupach***

	Type 1 diabetes		Control group	
	R	p-value	R	p-value
Age (years)	–0.265	0.022	–0.273	0.244
BW [kg]	–0.216	0.063	–0.323	0.165
FM [kg]	–0.265	0.022	0.021	0.930
FM% (%)	–0.110	0.349	0.215	0.362
Diabetes duration (years)	–0.095	0.416	–	–
HbA1c (%)	–0.072	0.538	–	–
INS/day [units/day]	–0.314	0.320	–	–
INS/kg [units/kg]	–0.034	0.772	–	–

BW — body weight; FM — total body fat mass; FM% — percentage value of the body fat mass; INS/day — daily insulin dose; INS/kg — daily insulin dose per kg of body weight

subjects in the control group than in patients with type 1 and type 2 diabetes, without a significant impact of age and sex on the obtained results [22].

Martos-Moreno et al. evaluated resistin concentrations in children in the early stages of type 1 diabetes before commencing insulin therapy, and after one and four months of treatment. Their results showed no difference, while the concentrations were similar to those obtained in the control group at all time points [23]. Furthermore, in the study by Celi et al., the resistin levels observed in children with type 1 diabetes were lower than in their healthy peers [24].

Resistinaemia in diabetic patients in our study presented significantly lower values than in the healthy subjects in the control group.

As resistin is one of the adipocytokines, we analysed its concentrations together with body fat mass, to then evaluate the mutual correlations.

In the studied group of children with type 1 diabetes, results obtained with bioelectrical impedance analysis showed similar body fat mass to those in the control group.

In both groups, a significant association between the fat mass and gender was confirmed, showing that its contents are higher among girls, while no gender-related differences in resistinaemia were found.

The lack of significant differences in terms of body fat mass between the children with diabetes treated with different methods (i.e. conventional, intensive functional insulin therapy, or continuous subcutaneous insulin infusion) and the presence of a positive correlation between fat mass and both the total daily insulin dose and the dose converted per kilogram of body weight, indicate the importance of total insulin dose sizes for adipose tissue mass gain, and not its distribution pattern throughout the day.

In the group of children with diabetes, no relationship was found between fat mass and metabolic control of the disease, assessed with the glycated haemoglobin value, but a positive correlation with age and duration of diabetes was demonstrated. In the control group, however, the dependence of fat mass on age did not reach statistical significance. This may suggest that the strong correlation between age and fat mass observed in children with diabetes is related to the disease dura-

tion, and thus to the chronic exogenous insulin therapy and peripheral hyperinsulinaemia.

Resistin is considered to be the adipocytokine the physiological role of which is to maintain the blood glucose level during hunger [13]. In patients with type 1 diabetes, due to the imperfections of treatment, hyperglycaemia is a common phenomenon. At high glucose serum concentrations, the hyperglycaemic effect of resistin, treated as 'redundant', may be subject to suppression by inhibiting its secretion. The mechanisms controlling production and secretion of resistin in the adipose tissue are not clear, although in adipocytes cultured *in vitro*, Haugen et al. observed a significant reduction in the amount of resistin mRNA under the influence of increasing concentrations of insulin [25]. This observation was consistent with the results of a study conducted by Liu et al. [26], thus hyperinsulinaemia, which frequently appears in patients with type 1 diabetes, could also exert an inhibitory effect on the secretion of resistin, resulting in its reduced levels in these patients.

In children with diabetes in the studied group, a negative correlation between resistin levels and body fat mass was demonstrated. Furthermore, a negative correlation between resistinaemia and age was observed. These results might be explained by the varied maturity of adipocytes. In the studies carried out on tissue cultures of human preadipocytes, resistin levels are high, while in the cultures of mature adipocytes they are very low [1, 4]. From this it follows that more resistin should be produced in less mature adipose tissue, with relatively more preadipocytes. An increased amount of adipose tissue and a more advanced age of patients may be associated with its greater maturity and, probably, lower secretion of resistin. However, this correlation was not found in healthy children, so the impact of type 1 diabetes should be considered. Despite the 'missing' correlation of resistin concentration and insulin doses, chronic hyperinsulinaemia in diabetic patients might be at least one of the factors influencing diminished serum resistin levels — insulin dose is not equal with insulin serum concentration, nor is its actual activity, when also insulin resistance and anti-insulin antibodies are taken into consideration.

There is an unresolved question whether the reduced serum resistin levels observed in children and adolescents with type 1 diabetes are related to disorders in insulin sensitivity — future research in this field should include simultaneous and objective evaluation of insulin resistance.

Conclusions

Type 1 diabetes mellitus induces diminished serum resistin concentrations in fasting children and adolescents. It also reveals a negative correlation between resistin levels and body fat mass, which was not observed in healthy children. These findings seem to result from broken physiological adipo-insular regulations in type 1 diabetes, independent of disease duration, its metabolic control and insulin supply. To clarify the exact mechanisms and possible relation to the state of insulin resistance, further investigations would be required.

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