Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Review Paper | Praca poglądowa
Pediatr Endocrinol Diabetes Metab 2017;23,2:96-100
DOI: 10.18544/PEDM-23.02.0079

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TOFI phenotype – its effect on the occurrence of diabetes

Fenotyp TOFI – jego wpływ na występowanie cukrzycy

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Abstract
Recent studies have reported a significant increase in the incidence of type 2 diabetes in the past 30 years. They also predict that this trend will continue. This is related to a change in lifestyle, which results in a parallel increase in the incidence of overweight and obesity. However, symptoms of the metabolic syndrome, so far closely related to abdominal obesity, are relatively common among people with normal body mass index (BMI) and waist circumference. The aim of the study is to present the TOFI phenotype (thin outside, fat inside) as an important factor in pathogenesis of type 2 diabetes. In the 1980s, the first study of the MONW (metabolic obese normal weight), a phenotype that is characterized by metabolic diseases in people with normal body weight. Since then, no uniform criteria have been established for MONW deployment, which has created difficulties in identifying affected individuals. Recent work has appeared describing the TOFI phenotype, which seems to lead to the appearance of MONW. People affected by this problem, in spite of undersized fatty tissue, have an increased amount of adipose tissue surrounding the internal organs, which increases the risk of insulin resistance and type 2 diabetes. In the diagnostics of the TOFI phenotype, magnetic resonance imaging is of paramount importance. Previous studies did not provide clear answers about the pathogenesis of TOFI nor which factors stimulate its development. Prophylaxis and treatment of the syndrome include increased physical activity, the promotion of correct eating habits, and a use of metformin.
Key words
diabetes mellitus , TOFI, obesity

Streszczenie
Wyniki badań wskazują na znaczący wzrost zapadalności na cukrzycę typu 2 w ciągu ostatnich 30 lat. Przewidują one również, że ta tendencja się utrzyma. Taki stan rzeczy ma związek ze zmianą stylu życia, z czego wynika równoległe zwiększenie częstości występowania nadwagi i otyłości. Jednak objawy zespołu metabolicznego, dotychczas ściśle wiązanego z otyłością typu brzusznego, pojawiają się stosunkowo często u osób z prawidłowym BMI (*Body Mass Index*) i obwodem w talii. Celem pracy jest przedstawienie fenotypu TOFI (*thin outside fat inside*) jako istotnego czynnika patogenezy cukrzycy typu 2. W latach 80. XX wieku pojawiły się pierwsze badania dotyczące MONW (*metabolic obese normal weight*), czyli fenotypu, który charakteryzuje się występowaniem chorób metabolicznych u osób z prawidłową masą ciała. Od tego czasu nie ustanowiono jednolitych kryteriów rozpoznania MONW, co przysparza trudności w wyodrębnieniu osób, których problem ten dotyczy. Ostatnio pojawiły się prace opisujące fenotyp TOFI, który, jak się wydaje, może doprowadzić do pojawienia się MONW. Osoby, których dotyczy ten problem, pomimo miernie rozwiniętej tłuszczowej tkanki podskórnej, mają zwiększoną ilość tkanki tłuszczowej otaczającej narządy wewnętrzne, co zwiększa ryzyko wystąpienia między innymi insulinooporności i cukrzycy typu 2. W diagnostyce fenotypu TOFI zasadnicze znaczenie odgrywa badanie rezonansem magnetycznym. Dotychczasowe badania nie przyniosły jednoznacznych odpowiedzi o etiopatogenezie TOFI ani o tym, jakie czynniki stymulują jego powstawanie. Profilaktyka i leczenie zespołu obejmuje zwiększenie aktywności fizycznej, promocje prawidłowych nawyków żywieniowych, a w niektórych przypadkach również stosowanie metforminy.
Słowa kluczowe
cukrzyca, TOFI, otyłość

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Received: 26.06.2017
Accepted: 19.09.2017
Conflict of interests: none declared.

Pediatr Endocrinol Diabetes Metab 2017;23,2:96-100

According to the World Health Organisation (WHO), in 2005 an estimated 217 million people had diabetes and it is 7 times more than in 1985. The WHO predicts that the number of people affected by this disease will increase to 366 million by 2030 [1]. As is well known, diabetes type 2 is strongly correlated with lifestyle, physical activity and diet. Obesity is a major risk factor of diabetes type 2 [2] and other chronic diseases, e.g. cardiovascular disease, non-alcoholic fatty liver disease and certain types of cancer [1]. The prominence of both obesity and diabetes has significantly increased since the 1990s [3]. Diabetes type 2 is currently one of the most important public health issues. The aim of this research is to present TOFI, as a factor in pathogenesis of diabetes mellitus.

Differences between MONW and TOFI phenotypes

One widely acknowledged way of preventing diabetes is maintaining proper body weight. Body mass index as an indicator has a major advantage of being very inexpensive to obtain. However, it is not effective at identifying risk of developing the metabolic syndrome as a result of increased VAT (visceral adipose tissue). It refers to individuals with normal body weight but presenting set of qualities widely associated with obesity (e.g. hypertension, hypertriglyceridemia) and occurring with physical inactivity and a low VO2max as 'metabolically obese but normal-weight' (MONW). Using MR can even show deposition of visceral adipose tissue. A lot of slim individuals have more visceral adipose tissue than overweight or obese persons. This subphenotype is called TOFI (thin outside, fat inside) and it has been detected in both sexes [4]. According to research ethics committee of Hammersmith and Queen Charlotte's and Chelsea Research Ethics Committee Hospital in London ratio of IAAT (intra-abdominal adipose tissue) and ASAT (abdominal subcutaneous adipose tissue) (IAAT/ASAT), it allows to extract individuals with an increased risk of the metabolic syndrome. After a thorough analysis of collected data, the proposed ratio of IAAT/ASAT should amount to more than 1.0 (males) or more than 0.45 (females) to recognize TOFI phenotype [5]. Clinical criteria of the diagnosis of MONW are much cheaper than MRI, but there are still no uniform rules. In the diagnostics the indicated investigation DEXA Full Body Composition Scan.

The authors of the first paper on this topic proposed diagnostic criteria which are presented in the table I. For the recognition of MONW it entitles to obtain 7 points on the above-mentioned scale. Other studies have concluded that BMI should be below 25 kg/m^2 or 27 kg/m^2, HOMA> 1.69, percentage of body mass>30%, area of visceral adipose tissue as per CT> 100 cm^2. A new indicator has been recently developed. TyG index was calculated as ln (fasting triglycerides (mg dl^{-1}) × fasting glucose (mg dl^{-1})/2). According to research on 7541 non-diabetic, normal weight individuals levels of TyG index are correlate with a higher risk of diabetes and others metabolic diseases. Above 8.82 for men and 8.73 for women values of TyG index can be recognized MONW [6]. Lack of uniform criteria is a significant problem to compare tests results.

Consequences

Identifying subjects classified as TOFI may be important, since there is a chance that they are at an increased risk of a metabolic disease, compared with more obese subjects with less visceral fat [4,5]. It has been recently suggested that in the development of insulin resistance and type 2 diabetes, accumulation of lipids outside the classical adipose tissue depots may be the critical factor [8] There is a link between ectopic storage of excess lipids and the metabolic syndrome[(9], which is associated with the risk of developing a cardiovascular disease and type 2 diabetes [10,11]. Subjects defined as TOFI have been described as being at a higher risk of developing insulin resistance and type II diabetes due to the fact that they have reduced physical activity/VO_2max, reduced insulin sensitivity and higher abdominal adiposity and a more atherogenic lipid profile. Another important characteristics observed in this cohort of subjects is elevated levels of liver fat. The distribution of the adipose tissue in different organs affects their functioning and the functions of the whole organism. The best example of this is the accumulation of fat in the liver. Recent studies have shown that 25–50 % of patients with steatosis subsequently became diabetics, suggesting that hepatic steatosis may have a direct causative effect on the development of diabetes [10,11]. Similarly, this has also been linked to the development of cardiovascular diseases (CVD). Excessive fat in the liver can subsequently lead to steatohepatitis and cirrhosis, which predisposes to hepatocellular carcinoma [11]. The frequency of non-alcoholic liver disease in Western countries is estimated at 6-30% [12]. People who have excess visceral fat have a significantly increased risk of developing chronic kidney disease. Diabetes is the most common cause of chronic kidney disease. The aforementioned diseases emphasize the clinical significance of TOFI. Many people who have BMI (body mass index) <25 but have excessively developed visceral fat, which cannot be seen in the usual physical examination, are exposed to many chronic diseases significantly decreasing the quality of life [13]. As described, these individuals can be young and display premature signs of insulin resistance, hyperinsulinemia, and dyslipidemia that may eventually increase their risk for the development of diabetes and cardiovascular disease. From a clinical perspective, the presence of these metabolic and cardiovascular diseases could go undetected for years due to the individual's young age and normal body weight, which may mask the need for early detection and treatment [13]. All TOFI-related complaints are more common among men (14%) than women (12%) [5,15].

Tabela I. Kryteria rozpoznania zespołu metabolicznej otyłości z prawidłową masą ciała (w modyfikacji autorów wg [7])
Table I. *Criteria of the recognition of the syndrome of metabolic obesity with the correct body mass (MOWN)(in own modification [7])*

Test parameter Oceniany parametr	Identified irregularities Zaburzenia	Points Punkty
Glucose concentration Stężenie glukozy	Type 2 Diabetes IGT IFG Pregnant diabetes	4 4 2 3
Triglyceride concentration Stężenie trójglicerydów	TG> 150 mg / dl and cholesterol HDL <35 mg / dl TG> 150 mg / dl TG: 100-150 mg / dl	3 2 1
Uric acid concentration Stężenie kwasu moczowego	> 8 mg/dl	2
Blood pressure Ciśnienie krwi	> 140/90 mm Hg 125–140/85–90 mm Hg	2 1
Medical history Przeszłość chorobowa	Polycystic ovary syndrome Ischemic heart disease <60. year	4 3
Family history Obciążenie rodzinne	Diabetes type 2, IGT 3 Hypertension <60. year 2 Hypertriglyceridemia 3 Ischemic heart disease <60	3 2 3 2
Presence of predisposing factors Czynniki predysponujące	Low birth weight <2.5 kg Low physical activity <90 min aerobic exercise in week	2 2
Body mass interview Zmienność masy ciała	Women: weight gain> 4 or 8 or 12 kg after 18 years Men: weight gain> 4 or 8 or 12 kg after 21 years	1–3 1–3
BMI	23–25 kg/m^2 25–27 kg/m^2	1 2
Waist circumference Obwód talii	Women: 71.1–76.2 cm Women > 76.2 cm Men: 86.3–91.4 cm Men > 91.4 cm	1 2 1 2
Ethnic affiliation to the group High risk Etniczne czynniki przynależności do grupy ryzyka		1–3

The ectopic fat hypothesis

The major subcutaneous and abdominal fat compartments, ectopic fat depots in the liver and skeletal muscle take part in the pathogenesis of insulin resistance, which is one of the causes of the metabolic syndrome. The ectopic fat hypothesis suggests that a lack of sufficient adipocytes and/or limited capacity results in excess adipose storage around tissues and organs such as the liver, heart, and kidneys. The mechanism of affection on tissue and organ function by ectopic fat accumulation is yet undiscovered [16].

Age and gender

Women have proportionally higher total adipose tissue located in the lower body and significantly higher percentage total and subcutaneous fat stores than the males. Men, on the other hand, are predisposed to an increased upper body fat accumulation. Women's higher percentage total and subcutaneous fat stores indicate an abrupt reduction in subcutaneous fat stores with the menopause as recorded in white females in the 46–55 years compared to 36–45 years groups[17]. Comparing groups of MONW and non-MOWN women with similar

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body mass index, MONW women showed a higher percentage of body fat, lower fat-free mass, lower physical activity energy expenditure, and lower peak oxygen uptake than non-MONW women.

Metabolic and behavioral characteristics

A higher level of relative body fatness, a cluster of sedentary physical activity behaviors and a lower level of dietary restraince were the factors implicated in the deleterious metabolic profile of this unique at-risk population. Both metabolic and dietary behavioral variables are independently associated with TOFI. TOFI phenotype displays lower insulin sensitivity, potentially due to a cluster of sedentary behavior patterns that contribute to higher levels of adiposity. Dietary restraint may play a role in regulating insulin sensitivity [18].

Low body birth weight

Ruderman et al. observed that prevalence in the family type 2 diabetes, hypertriglyceridemia, hypertension or coronary disease especially at a young age – below 60 years old increases probability of MONW in non-obese members of this family. Ruderman et al. suggest that another factor that increases the risk for the occurrence of MONW is low birth weight. Other publications show that low birth weight is probably a factor risk factor of the metabolic syndrome among individuals with android obesity. Research of Conus et al. did not confirmed the existence of differences in average body weight during the neonatal period between adults with MONW and healthy people. Up to now, there areis no unequivocal data indicating whether low birth weight predisposes to the occurrence of MONW in cases where the person these keep the correct weight as adults [18–20].

Prophylaxis and treatment of the TOFI phenotype

Obesity, as a chronic disease, is usually treated for years or even for life. The motivation, constant control of the physician, support of a dietitian or physiotherapist is required [21]. The task becomes more complicated when physician have to work with a problematically obese patient who is not visually obese and seems to be healthy and without a risk of cardiovascular and metabolic diseases. According to the guidelines of obesity treatment the therapy should be based on nutrients, use of a balanced energy reduced diet, increase of physical activity to 150 minutes per week [22, 23]. Some patients require pharmacological support; those who have eating disorders (caused by night eating, stress, etc.). Currently in Poland, the only drug that is used in the obesity treatment is orlistat which inhibits the selective function of pancreatic lipase and the absorption of the fats from the gastrointestinal tract [24]. The therapeutic dose is 120 mg 3 times daily in real time meals, nevertheless there are no studies on the use of orlistat in TOFI phenotype. In the pharmacological treatment of obesity, attempts are made to inhibit serotonin reuptake and to inhibit noradrenaline and dopamine reuptake and anti-epileptic [25]. In addition, insulin-reducing drugs, such as biguanides and thiazolidinediones, are being introduced in the treatment of obesity [26]. In the study Diabetes Prevention Program, diabetes increased by more than 30% the risk reduction for diabetes using metformin in patients with BMI> 25 [27]. The risks of type 2 diabetes or cardiovascular disease increase when patients have the metabolic syndrome but it can be reduced by implicating changes into a life style. Persons who are not routinely diagnosed for metabolic disorders are invariably not predisposed for cardiovascular diseases and diabetes type 2 [18]. Treatment of insulin resistance in patients with a daily diet as opposed to individual and physical needs [28]. Some authors have suggested metformin, by undertaking its efficacy in improving insulin sensitivity for apparently unobservable female patients with polycystic ovary syndrome [26]. TOFI patients are not eligible to prevention programs so far. There are also no studies and data on TOFI patients both in Poland and in the other countries.

Summary

Obesity and type 2 diabetes are civilization diseases, whose morbidity is increasing year by year. For some time there has been an increased occurrence of insulin resistance or type 2 diabetes in people with normal BMI and waist circumference. This is connected with the occurrence of the TOFI phenotype, in which potentially lean and healthy people have increased visceral fat. It is also important to mention MONW phenotype, which besides the visceral fat deposit is characterized by the presence of elements of the metabolic syndrome, which includes hypertension, hypertriglyceridaemia and hyperglycaemia. The diagnosis of diabetes mellitus and other metabolic disorders in people with TOFI is challenging because the image of a lean patient with visceral obesity does not suggest the occurrence of any medical condition. One of the methods used for the diagnosis is MR, which measures the volume of adipose tissue stored around the internal organs. Also, the use of IAAT (intra-abdominal adipose tissue) and ASAT (IAAT / ASAT) allows to extract individuals with increased risk of metabolic syndrome. However, there areis still no uniform criteria suggesting the diagnosis of MONW or TOFI. According to the hypothesis of ectopic fat, the most responsible for the development of insulin resistance is fat accumulated around the liver, skeletal muscles, and kidneys. It is estimated that TOFI occurs in 14% of men and 12% of women. Other hypothesis suggests that low birth weight is a predisposing factor for MONW and TOFI, but other sources indicate a greater effect of lifestyle on adult subjects than perinatal morbidities in these patients. Currently, the TOFI phenotype is treated as obesity, therefore, while dealing with obese patients, attention is paid to

the appropriateness of diet and regular physical activity in the prevention and treatment of TOFI. Some specialists propose the introduction of pharmacological treatment with orlistat as a fat absorption inhibitor and CNS drugs such as SSRIs. Until now, no studies have been conducted with the above-mentioned drugs in patients with TOFI phenotype. References in the literature on the use of biguanides in this group of patients in the prevention of insulin resistance have been reported in the literature, but no studies have yet been performed in a larger group of patients.

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