Family Medicine & Medical Science Research

Chwalba and Otto-Buczkowska, Fam Med Med Sci Res 2014, 3:4
DOI: 10.4172/2327-4972.1000148

Review Article Open Access

Metabolic Syndrome is the Problem in Young Diabetics?

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Rec date: Nov 19, 2014; **Acc date:** Nov 25, 2014; **Pub date:** Nov 27, 2014

Summary

Metabolic syndrome is an important problem in a population of children and adolescents. Genetic predisposition and environmental factors such as physical inactivity and increased caloric intake are responsible for the predisposition to metabolic syndrome. Insulin resistance is proposed to have a pivotal role in the development of the metabolic syndrome

Metabolic syndrome, which is composed of such factors as insulin resistance, glucose intolerance or diabetes, dyslipidemia and arterial hypertension, contributes to accelerated development of cardiovascular diseases, orthopaedic disorders, and other medical consequences. Early conservative intervention with diet, exercise, and behavioural therapy may prevent the complications of insulin resistance.

Keywords: Insulin resistance; Metabolic syndrome; Hypertension; Dyslipidemia; Glucose intolerance

Introduction

The metabolic syndrome is also referred to as Insulin Resistance Syndrome (IRS) because of its essential feature - insulin resistance [1-6]. Insulin resistance may be the result of insulin receptors abnormalities (receptor insulin resistance) as well as be related to irregularities within the post-receptor signal system (post-receptor insulin resistance). The reduction of peripheral tissues sensitivity to insulin refers mainly to those ones being directly insulin sensitive.

Currently, much attention is being paid to the lipotoxic theory of the development of insulin resistance which assumes that the abnormalities of fatty acids metabolism result in excessive accumulation of lipids in muscle, liver and pancreatic β cells. This phenomenon known as "lipotoxicity", leads to the development of insulin resistance in muscle and liver, as well as to the impairment of β-cell function. Increased influx of FFA (free fatty acids) contribute to the deterioration of insulin sensitivity by stimulating gluconeogenesis and the weakening of the suppressive effect of insulin on hepatic glucose production. Fatty acids have a direct effect on the activity of insulin-sensitive glucose transporter 4 (GLUT4), as well as on its movement.

In clinical research, the relationship between insulin resistance and cardiac hypertrophy has been studied. Increased fat accumulation in the perivascular space is also very important. It is believed that the insulin resistance occurs in genetically predisposed individuals, experiencing certain environmental factors – which shows its epigenetic base. Epidemiological research documenting the differentiated prevalence of insulin resistance in different ethnic populations and noting family predisposition to the development of diseases associated with impaired insulin sensitivity suggest a genetic base of insulin resistance. Currently, it is believed that the development of insulin resistance may depend largely on genetic factors [7]. The main environmental factors associated with the development of insulin resistance include reduction in physical activity and access to the diet rich in calories, rich in foods with high glycemic index. Reduced physical activity is an important factor in intensifying insulin resistance [8-11]. Among the environmental factors, the disorders of fetal development have been also mentioned. In children, born with too low weight in relation to gestational age (small for gestational age - SGA), insulin resistance and other features of the metabolic syndrome have been more frequently observed than in children with normal birth weight [12-15]. On the other hand, children born with very high birth weight are also prone to obesity and insulin resistance [16-19]. The consequence of insulin resistance is an excessive stimulation of β cells and the increase of endogenous insulin secretion for the maintenance of glucose homeostasis. This leads to a gradual reduction in the number of these cells resulting in impairment of glucose tolerance. The International Obesity Task Force report from 2005 indicates that nowadays one out of every five children is overweight or obese [20]. Investigators from the Bogalusa Heart Study reported a prevalence of 3.6% in youth 8-17 years of age [21]. The persistence of obesity from childhood and adolescence into young adulthood has been shown in a number of studies [22,23]. It is known that obesity is a cause of early development of arteriosclerosis and its cardio-vascular complications in adult life [24].

Assessment of Insulin Sensitivity

Different indicators have been used to assess the sensitivity to insulin, but hyperinsulinemiceuglycemic clamp is the "gold standard" for insulin sensitivity determining. However, this is the method used for scientific purposes. Population research in patients with a preserved ability to insulin secretion uses simpler indirect methods based on the evaluation of the relationship between insulin concentration and fast blood glucose or during the oral glucose load test: FGIR index (fasting glucose-to-insulin ratio), HOMA-IR index (Homeostasis Model Assessment - Insulin Resistance).

Metabolic Syndrome in Adolescent Patients

Until recently it was thought that the occurrence of the metabolic syndrome is specific for patients not younger than 16 years of age. At the moment, we know that many of the features of this syndrome can be found in younger groups of children and adolescents, and in high-risk groups, full-blown metabolic syndrome is diagnosed in children even under 10 years of age [25-28]. As already mentioned, insulin resistance underlies the metabolic syndrome. It is a consequence of the accumulation of excessive adipocytes number in the body. A preferential site of fat accumulation is the abdominal-perivisceral region. With a positive caloric balance, adipocytes undergo excessive

hypertrophy, which causes adipocyte dysfunction, as well as adipose tissue endocrine and immune responses. As a consequence, more free fatty acids (FFA) are released into the portal system. Excess of circulating FFA, TNF-α and other factors induces insulin resistance [29]. It was found that insulin resistance resulting from obesity is partly associated with the inflammatory process of low activity ongoing in adipose tissue. Recent years have brought information about the role of retinol binding protein (RBP4: retinol-binding protein 4) in the development of insulin resistance. It was found that RBP4 causes the development of insulin resistance in both liver and skeletal muscle [30-32]. Recently, Rhie et al. have presented the results of their research in the group of slim, overweighed, and obese children [33]. They found the dependence of RBP4 levels on the stage of puberty, BMI and triglyceride levels and no correlation with HOMA-IR. The authors believe that the association of RBP4 levels with the degree of insulin resistance is secondary to the relationship between RBP4 levels and the amount of fat in the body. This is confirmed also by other authors [34]. These data suggest that RBP4 may be an early marker of insulin resistance being important also in children. The action mechanism of this protein is not fully understood and the role of RBP4 in the pathogenesis of insulin resistance requires further research.

Criteria for Diagnosis of Metabolic Syndrome

Selection of the criteria for the diagnosis of metabolic syndrome in adolescents has been still discussed [35-45]. However, generally accepted model combines the presence of increased waist circumference, triglycerides and cholesterol HDL, insulin secretion and behavior of blood pressure [46].

The waist-height ratio (WHtR) is a simple and effective screening tool that can be used to identify obese children with the metabolic syndrome. The WHtR is the simplest index to calculate and interpret, making it an ideal non-invasive screening tool to use in clinical practice [47,48].

The Occurrence of the Metabolic Syndrome in Children with a History of Cancer

Korean authors, on the basis of their own observations, drew attention to the need for careful control of metabolism, including adipose tissue measurement and prevention of metabolic syndrome in children with a history of cancer [49]. In the course of the metabolic syndrome in children, non-alcoholic fatty liver disease (NAFLD: Non Alcoholic Fatty Liver Disease) has been increasingly found. This disease is associated with a significantly higher mortality, as well as with an increase in diseases in the cardiovascular system [50]. NAFLD is a disease associated with excessive accumulation of fat, particularly within the abdominal cavity. Monteiro et al. in a research conducted in a sample composed of 145 subjects, aged 11 to 17 years, pointed out the usefulness of indicators such as assessment of waist circumference (WC), trunk fat mass (TFM) and fat mass (FM) by dual-energy X-ray absorptiometry (DXA) and ultrasound (US) for diagnosis of NAFLD [51]. Their findings indicated that TFM, IAAT and WC present high potential to identify NAFLD in obese children and adolescents. During the last decade, paediatricians have observed a dramatic increase of metabolic syndrome and NAFLD in children. Genetic susceptibility and the pressure of intrauterine environment and lifestyle are all crucial to activate molecular machinery that leads to development of NAFLD and MS in childhood. Central obesity and consequent adipose tissue inflammation are critical to promote both MS-associated metabolic dysfunctions and NAFLD-related hepatic damage [52]. Deposition of lipids in the liver can cause liver resistance to insulin, which may correlate with other disorders characteristic to the metabolic syndrome as dyslipidemia, impaired glucose metabolism, hypertension [53,54]. NAFLD syndrome is asymptomatic, hence the need to monitor its prevalence in adolescent patients with signs of insulin resistance.

Polycystic Ovary Syndrome (PCOS) has increasingly been diagnosed in girls. It is also often associated with the occurrence of the metabolic syndrome. A characteristic feature is the presence of insulin resistance, which often leads to impaired glucose tolerance, as well as to clinically overt diabetes [55-58]. Left ventricular mass index (LVMI) can be used as a tool in predicting the presence of metabolic syndrome and its associated risk of diseases in the cardiovascular system [59]. Bostanci et al. in their research showed that LVH occurs commonly in pediatric MS and is associated with systolic hypertension and insulin resistance [60]. The authors believe that LVMI should be measured routinely for the predicting of cardiovascular risks in these patients. To assess the threat of cardiovascular complications in adolescents with metabolic syndrome it is also used the assessment of carotid intima-media thickness (IMT) which is a potential indicator of subclinical atherosclerosis in patients with metabolic syndrome (MS). Epicardial Adipose Tissue Thickness (EATT) is suggested as a new cardio metabolic risk factor. Assessment of EATT and carotid IMT in routine echocardiographic examinations is suggested as a feasible and reliable method for the evaluation of obesity with MS and its related cardiovascular risks in children and adolescents [61].

In considering the causes of the syndrome in children, attention should be paid to the report of the Greek authors, who drew attention to the role of chronic stress in the development of the metabolic syndrome [62].

Insulin Resistance and Metabolic Syndrome in Type 1 Diabetes

It was previously thought that the essence of type 1 diabetes was a progressive insulin deficiency resulting from a progressive self-destruction of β-cells, whereas the sensitivity to insulin operation was maintained. Today, we already know that insulin resistance is also present in type 1 diabetes [63-66].

Insulin resistance is related to a variety of factors including the stage of life development, since during puberty we deal with so-called "physiological" insulin resistance. In these patients the overweight plays also an important role in insulin resistance increase. Overweight of the patients with type 1 diabetes is often the result of the "over insulining". The patients try to maintain normal blood glucose profile by increasing the dose of insulin. It leads towards "vicious circle". Increasing of insulin doses without reduction of caloric intake results in an increase of adipose tissue mass and consequently in increase of the insulin resistance. This increased insulin resistance causes the need to increase the dose of insulin and so on. Interruption of this "vicious circle" requires radical changes in nutrition and lifestyle. Limitations are required in caloric intake, including a reduction of carbohydrates in the diet of <40% and increase in physical activity [67,68]. Insulin resistance plays an important role in development of angiopathy in patients with impaired carbohydrate metabolism [69].

Hypertension may be a signal of changes in the cardiovascular system, we must remember however that there can be only discreet

pressure increases [70,71]. Values that are at the upper limit of the normal for a given age require already very careful consideration and usually implementation of the treatment. Pressure measurement in children and adolescents requires a great care, the results should be evaluated using the centile charts [72]. When interpreting the results, in addition to gender, age and height, body weight should also be taken into account if anthropometric data goes beyond the 90 percentile for a given age. The results of blood pressure measurements in adolescent patients with type 1 diabetes presented by Pietrzak et al., showed a significant relationship between blood pressure and body mass index and the percentage of adipose tissue in the body [73]. The results of the tests concerning adolescent patients with type 1 diabetes presented by Dutch authors showed a significant increase in risk factors for damage to cardiovascular system in patients who are overweight or obese in comparison to those with due weight [74]. This is also confirmed by other authors [75].

Disfunction in glucose metabolism causes worsening of cellular response to insulin associated with an increased cardiovascular risk. Miniello et al. in their study conducted in a group of 150 children and adolescents confirmed common carotid intima-media thickness (cIMT) was positively related to age, BMI, waist circumference and triglycerides; antero-posterior diameter of infra-renal abdominal aorta (APAO) measurements revealed positive correlation with age, BMI, waist circumference, triglycerides, C-reactive protein, fasting insulin and HOMA index [76]. HOMA index increase induced a worsening in endothelial function since childhood.

Family history of diabetes and prediabetes plays an significant role in relation to patients outcome and cardiovascular risk profile. Pannacciuli et al. evaluated the effect of first-degree family history of type 2 diabetes in intima-media thickness of common carotid artery (IMT-CCA) in a group of 401 individuals aged 18-45 with normal glucose tolerance. 213 subjects had no family history of type 2 diabetes until the third generation (FH(-)) and 188 subjects had a family history as having one or both parents with type 2 diabetes (FH(+)). IMT-CCA and 1- and 2-h postchallenge glucose concentrations were significantly higher in the group of patients with FH(+) than in FH(-); also IMT-CCA was positively related with age, BMI, triglycerides, waist circumference, blood pressure, basal glucose level, 1- and 2-h post challenge glucose concentrations and HOMA(IR) [77]. Authors study indicates that a genetic predisposition to type 2 diabetes, in association with slightly raised glucose level may probably accelerate atherosclerosis development and increase the risk for coronary heart disease in glucose-tolerant population.

Some authors suggest some clinical settings that are associate with insulin resistance are beyond of metabolic syndrome. Berezin et al. assessed a relationship between insulin resistance and counts of CD45(-)CD34(+), CD14(+)CD309(+), and CD14(+)CD309(+)Tie2(+) phenotyped circulating endothelial progenitor cells (EPCs) in patients with ischemic chronic heart failure (CHF) [78]. Population of 300 patients suffering from CH aged 48-62 with coronary artery disease confirmed in angiography and/or with previously defined MI were involved. As a result it was observed that Circulating EPCs counts were statistically significantly lower in CHF patients with IR than in patients without IR; the most valuable predictors of the depletion of the CD45(+)CD34(+) EPCs were NT-pro-brain natriuretic peptide (BNP), left ventricular ejection fraction, NYHA class, NT-pro-BNP. IR may be an additional factor contributing decreased circulating level of proangiogenic EPCs in non-diabetic CHF patients. Another authors, Doehner et al. pay attention to metabolic impairment in cardiovascular diseases and highlight growing appreciation of the complexity of metabolic aspects of HF pathophysiology [79]. The authors reviewed recent evidence on myocardial and metabolic impairment in HF. According to the conclusions, myocardium, peripheral tissues and organs are involved and affected by metabolic failure. This condition results in the lack of global balance between catabolic and anabolic signals, what leads to tissue wasting and to cachexia. Gouya et al. aimed to evaluate connection of the nutritional condition by using nutritional risk index (NRI) with metabolic and inflammatory biomarkers and apetite –regulatory hormones in the group of patients with HFas well as to analyse its prognostic value. The study involved 137 stable chronic HF patients; median age 60 years, median BMI 27 kb/m(2) on optimized medical treatment. Baseline NRI of < 113 was associated with an increase in the levels of ghrelin, peptide YY, tumour necrosis factor-alpha, adiponectin and the N-terminal prohormone of brain natriuretic peptide compared with those in patients with NRI of ≥ 113. The NRI was correlated with the homoeostasis model assessment of insulin resistance index and correlated with the NT-proBNP level. The overall mortality rate was 20%. A baseline NRI of < 113 was associated with a higher risk of all-cause mortality [80].

Description of Cases

Case 1

18-year-old boy born with birth weight of 2800 g in good condition. Starting from preschool times, he showed accelerated weight gain. He was not sick. When he was 18 years old the fainting incident occurred, high blood pressure was found, he was sent to cardiac clinic and discharged with a diagnosis of "hypertension under observation." Due to elevated blood glucose the patient was sent for consultation to the diabetes clinic. During the first visit: weight 84.5 kg, height 176 cm; BMI 28 kg / m^2; BP 140/70 mmHg. Oral glucose tolerance test was performed. Blood glucose concentration 0' 5,7 mmol/l; 120' 11,6 mmol/l; insulin 0' 12,3 μU/ml; 120' 137,0 μU/ml; C-peptide is 2.06 ng / ml; HbA1c 6.1%.

The clinical picture suggested the diagnosis of early stage of metabolic syndrome. Low birth weight, developing obesity, hypertension occurrence with no apparent reason, impaired glucose tolerance with increased insulin secretion suggest the early stage of the developing metabolic syndrome. Since the basis of this syndrome is insulin resistance, dietary treatment, and increasing of physical activity, blood glucose monitoring and blood pressure control were recommended. Metformin preparation was included. After 3 months, during the follow-up visit there were decreases in body weight of more than 7 kg (77.2 kg), blood pressure 140/80 mmHg. Control curve: glucose 0 ' 5.6mmol / l; 120 ' 10.8 mmol / l; C-peptide is 6.17 ng / ml; lipids within the range of normal. HbA1c 6.0%. It was recommended to increase the dose of metformin, maintain the diet and make a follow-up visit in half a year. Periodic phone contact was recommended. BP test with the use of Holter and cardiac monitoring was scheduled.

Case 2

15-year-old boy, negative family history of diabetes. In an interview with asthma treated with steroids in early childhood, currently the patient is not receiving such drugs. Obesity from early childhood, now: weight 89.5 kg > 97 pc; height 173 cm 50-75 pc; BMI 29 kg / m^2> 97 pc. Due to the polydipsia and polyuria, the concentration of glucose

was marked showing hyperglycemia (above 16.7 mmol / l), the boy was sent to the diabetes department. At admission good general condition, only moderate dehydration was found. On the basis of clinical picture and preliminary tests (blood glucose 16.9 mmol / l, glucosuriaand acetonuria, normal gas analysis, marked a slight degree of dyselectrolytemia) hydration was performed and insulin treatment included (first by infusion and then by multiple injections). Daily blood pressure measurement with Holter was made showing circadian rhythm abnormality (Non-Dipper). After a few days, the normalization of glycemia was obtained and the boy was discharged home with the recommendation of the use of a calorie-restricted diet, the use of self-monitoring, insulin administration by multiple injections (fast- and long-acting analogue). Due to the high degree of obesity, taking into account the presence of insulin resistance, metformin preparation was included. The first visit to the outpatient diabetes clinic had place after 6 weeks from the discharge date. A very marked reduction in insulin requirement was found. It was recommended to use only a single dose of long-acting analogue and administration of metformin. During the next visit, after 6 weeks the boy's condition was good. Highly significant reduction in body weight (weight 73.4 kg, height 177.5) was noticed. HbA1c level of 6.1%; balanced glucose levels. The continuation of one very low dose of analogue and metformin preparation was recommended. In the meantime, the results of tests were obtained - C-peptide 0.81 ng / ml; autoantibodies moderately elevated a / GAD 49.7 U / ml; ICA 20j IDF; IA2 47.6 U / ml. TSH 2,091 mU / l; ATG antibodies <20 IU / ml; ATA 21 IU / ml. Lipids: total cholesterol 154 mg / dl; HDL 32 mg / dL; TG 158 mg / dL.

In this case, type of diabetes differentiation faces some difficulties. Phenotype (very high degree of overweight, bordering on obesity), associated disturbances of circadian blood pressure profile, as well as dyslipidemia may speak for the diagnosis of type 2 diabetes in the course of the metabolic syndrome. This diagnosis can be supported by quick reduction of the need for insulin, possibly associated with body weight reduction, and normal levels of C-peptide. However, rapid increase of dehydration signs going together with acetonuria at diagnosis draws attention because it is usually associated with type 1 diabetes and then elevated titers of autoantibodies. This would indicate diabetes type 1 with autoimmune basis. It seems that at the present time it should be taken into consideration a hybrid form or as some authors define it the type 1.5 diabetes. It is necessary to monitor the effects of treatment, the level of C-peptide and autoantibodies. In this case, the final differentiation of diabetes type may be possible after a longer follow-up.

Case 3

15-year-old girl, at 14 years of age she was sent to the diabetes department due to glucose intolerance. At admission significant obesity drew attention (weight 59.6 kg, height 151.8 cm, BMI 25.86 kg / m2> 97 pc); hirsutism signs. Performed tests showed elevated levels of glucose (9.5 mmol / l) in the second hour of OGTT and high insulin level 214.8 uU / ml. Signs of dyslipidemia were found; total cholesterol. 210 mg / dl; HDL 42.9 mg / dl; TG 202 mg / dL. TSH 4,66mU/l. Systolic blood pressure and diastolic blood pressure of 90-95 pc. Due to the lack of menstruation and hirsutism signs, the test in the direction of the polycystic ovary syndrome were performed confirming the diagnosis of PCOS. In this case, it may be assumed the diagnosis of the metabolic syndrome (obesity, hyperinsulinemia indicating insulin resistance, hypertension, dyslipidemia, in the course of PCO). Metformin preparation was used in the treatment. The girl is under the care of a gynecological, endocrine and diabetes outpatient clinic. Test OGTF performed after one year and a half of the treatment showed persistence of carbohydrate metabolism disorders with impaired glucose tolerance and hyperinsulinemia after glucose load (glucose 0 ' 5.1 mmol /L; 60' 12.1 mmol /l; 120 ' 8.7 mmol / l; insulin 0 ' 18.0 uU /ml; 60' 272 uU / ml; 120 ' 282.7 uU /ml; C-peptide 2.45 ng / ml), HbA1c 6.8%. Body weight decreased (50.1 kg, an increase in 153 cm). It was recommended to increase the dose of metformin. The girl menstruates when using hormonal drugs.

Discussion

The cases represent a diverse clinical picture.

In the first case (Case 1), the first observed symptom of the disease was hypertension diagnosed as "Hypertension under observation." In the course of diagnostic tests designed to determine the cause of hypertension, elevated levels of glucose in the blood was found. Given the overweight, the test in the direction of the metabolic syndrome were performed. The results of these tests were in favor of the diagnosis of early-stage of metabolic syndrome. This diagnosis is supported by the presence of obesity, high blood pressure, and elevated levels of glucose and insulin in the blood, which were showed by OGTT test.

In the second case (Case 2), the first symptom do draw attention was diabetes. The method of multiple injection was used in the insulin treatment. It has also been found disorders of circadian arterial blood pressure profile. Due to the obesity and insulin resistance signs metformin was included. Further observation and tests results did not gave way to unequivocal determination of the type of diabetes. Further diagnostics is necessary. Because of the signs of the metabolic syndrome (obesity, diabetes, dyslipidemia, disorders of circadian rhythm of blood pressure) metformin therapy was continued.

Another case (Case 3) was a girl with a diagnosis of polycystic ovary syndrome (PCOS) with signs of the metabolic syndrome (obesity, glucose intolerance, hyperinsulinemia, dyslipidemia, elevated blood pressure). In the treatment it was recommended the continuation of metformin and weight control. This diversity of presented cases indicates the need to take into account the diagnosis of the metabolic syndrome also in adolescent patients.

Conclusion and Summary

Recent years have brought more and more reports about the threat of metabolic syndrome already in groups of small children. This problem is of particular importance in adolescents, where the risk factors of this syndrome occurrence associated with genetic determinants and growing epidemic of childhood obesity go together with so-called "physiological" insulin resistance associated with the puberty. A relatively new issue is the presence of the metabolic syndrome in adolescent patients with type 1 diabetes.

The analysis of the reports on the long-term effect of obesity in children carried out by British authors showed a significant effect of overweight and obesity occurring in childhood and adolescence to an increase of health treats in adulthood [81]. Danish authors proved the existence of a linear relationship between the values of BMI in childhood and the risk of ischemic heart disease development in adulthood [82]. Other authors also pointed out the risk of early occurrence of coronary heart disease (CHD) in adolescent with overweight [83].

Therefore, it is so important to monitor carefully these processes already in the youngest children starting from infancy [84].

Many features of metabolic syndrome can be observed in younger groups of children and adolescents; full-blown metabolic syndrome is diagnosed in children even under 10 years of age [25-28].
RBP4- retinol-binding protein 4- plays an important role in the development of insulin resistance in both liver and skeletal muscle [30-32].
RBP4 level is dependent on the stage of puberty, BMI and triglyceride levels; no correlation with HOMA-IR; the association of RBP4 levels with the degree of insulin resistance is secondary to the relationship between RBP4 levels and the amount of fat in the body [33].
RBP4 may be an early marker of insulin resistance being important also in children [34]
There is a need in children with a history of cancer for careful control of metabolism, adipose tissue measurement and prevention of metabolic syndrome [49].
NAFLD -Non-alcoholic fatty liver disease- has been found in the course of the metabolic syndrome in children; NAFLD is associated with a significantly higher mortality and with an increase in cardio-vascular diseases [50].
Indicators such as assessment of waist circumference (WC), trunk fat mass (TFM), fat mass (FM) by dual-energy X-ray absorptiometry (DXA) and ultrasound (US) are useful for diagnosis of NAFLD [51].
As NAFLD syndrome is asymptomatic, there is the need to monitor its prevalence in adolescent patients with signs of insulin resistance.
Polycystic ovary syndrome (PCOS) diagnosed in girls is also often associated with the occurrence of the metabolic syndrome
Left ventricular mass index (LVMI) can be used as a tool in predicting metabolic syndrome and its associated risk of cardiovascular diseases [59].
Left ventricular mass index (LVMI) can be used as a tool in predicting metabolic syndrome and its associated risk of cardiovascular diseases [59].
Insulin resistance is also present in type 1 diabetes [63-66].
Type 1 diabetes patients overweight is often the result of the "overinsulining". [67,68].

Table 1: Main findings of the literature studies considered in the manuscript

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