ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2022 April 15; 13(4): 282-386

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

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Monthly Volume 13 Number 4 April 15, 2022

World Journal of Diabetes

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ABOUT COVER

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The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJD* as 3.763; IF without journal self cites: 3.684; 5-year IF: 7.348; Journal Citation Indicator: 0.64; Ranking: 80 among 145 journals in endocrinology and metabolism; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

PUBLICATION DATE
April 15, 2022

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2022 April 15; 13(4): 282-307

DOI: 10.4239/wjd.v13.i4.282

ISSN 1948-9358 (online)

REVIEW

Insulin-resistance in paediatric age: Its magnitude and implications

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Specialty type: Pediatrics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Herold Z, Hungary; Liao JX, China; Wang CR, Taiwan

Received: February 18, 2022
Peer-review started: February 18, 2022
First decision: March 11, 2022
Revised: March 12, 2022
Accepted: March 27, 2022
Article in press: March 27, 2022
Published online: April 15, 2022

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Abstract

Insulin resistance (IR) is insulin failure in normal plasma levels to adequately stimulate glucose uptake by the peripheral tissues. IR is becoming more common in children and adolescents than before. There is a strong association between obesity in children and adolescents, IR, and the metabolic syndrome components. IR shows marked variation among different races, crucial to understanding the possible cardiovascular risk, specifically in high-risk races or ethnic groups. Genetic causes of IR include insulin receptor mutations, mutations that stimulate autoantibody production against insulin receptors, or mutations that induce the formation of abnormal glucose transporter 4 molecules or plasma cell membrane glycoprotein-1 molecules; all induce abnormal energy pathways and end with the development of IR. The parallel increase of IR syndrome with the dramatic increase in the rate of obesity among children in the last few decades indicates the importance of environmental factors in increasing the rate of IR. Most patients with IR do not develop diabetes mellitus (DM) type-II. However, IR is a crucial risk factor to develop DM type-II in children. Diagnostic standards for IR in children are not yet established due to various causes. Direct measures of insulin sensitivity include the hyperinsulinemia euglycemic glucose clamp and the insulin-suppression test. Minimal model analysis of frequently sampled

intravenous glucose tolerance test and oral glucose tolerance test provide an indirect estimate of metabolic insulin sensitivity/resistance. The main aim of the treatment of IR in children is to prevent the progression of compensated IR to decompensated IR, enhance insulin sensitivity, and treat possible complications. There are three main lines for treatment: Lifestyle and behavior modification, pharmacotherapy, and surgery. This review will discuss the magnitude, implications, diagnosis, and treatment of IR in children.

Key Words: Insulin resistance; Children; Diabetes mellitus; Obesity; Genetic; Acquired

Core Tip: Insulin resistance (IR) increases in children due to lifestyle changes and the pandemic of obesity. There is a strong association between obesity in children and adolescents and IR. There is a broad range of genetic and acquired causes of IR with a wide variability of its prevalence from one country to another. Many available tests can directly or indirectly estimate IR. To prevent future IR, we should target all the factors that could help the development of IR, especially obesity.

Citation: Al-Beltagi M, Bediwy AS, Saeed NK. Insulin-resistance in paediatric age: Its magnitude and implications. *World J Diabetes* 2022; 13(4): 282-307
URL: https://www.wjgnet.com/1948-9358/full/v13/i4/282.htm
DOI: https://dx.doi.org/10.4239/wjd.v13.i4.282

INTRODUCTION

Initial data suggest that insulin resistance (IR) is becoming more common in children and adolescents than before. IR is insulin failure in the normal plasma levels to adequately stimulate glucose uptake by the peripheral tissues such as adipose tissues and skeletal muscle, inhibit the hepatic gluconeogenesis and release of glucose into circulation, and/or suppress the output of very-low-density lipoprotein[1]. IR is a spectrum disorder that ranges from very mild to very high resistance and is commonly associated with obesity. Consequently, chronic hyperinsulinemia occurs as a compensatory mechanism to IR[2]. There is a strong association between obesity in children and adolescents, IR, and the metabolic syndrome (MS) components, including the high risk of cardiovascular complications[3]. IR syndrome (IRS) is characterized by the presence of hyperinsulinemia and one or more of the following: impaired glucose tolerance, central obesity, hypertension, hirsutism, hypertriglyceridemia, hypercholesterolemia, reduced high-density lipoprotein, high low-density lipoprotein, hyperuricemia, coagulation abnormalities favoring thrombosis, polycystic ovary syndrome and/or menstrual disturbances[4]. Table 1 shows various forms of IR.

EPIDEMIOLOGY OF IR IN CHILDREN

IR is rising due to increasing obesity among children and adolescents, changing the lifestyle with lack of physical activities, high-calories intake (western diet style), overdependence on the technology with more sedentary life due to TV watching, and social media addiction. Although IR usually occurs in obese people, not all obese people have IR. It may also occur in normal physiological status during puberty or pregnancy[5]. IR may appear as early as two years of age in children with certain genetic predisposition and environmental influences (*e.g.*, decreased activity) with a peak at puberty due to increased growth hormone secretion[6]. IR prevalence in children varies from one country to another depending on many factors, including genetic, racial, and environmental factors, and due to the heterogeneity of the methods of data collection and the cut-off values used to define IR. In a systematic review study by van der Aa *et al*[7], the overall prevalence rates of IR ranged between 3.1% and 44% of children and adolescents, being more prevalent in girls than boys due to their earlier pubertal changes. They also found that IR reached 68.4% in obese boys. Jurkovičová *et al*[8] show an IR prevalence rate of 18.6% in Slovakian adolescents with significant association with insufficient physical activity, low level of physical fitness, a small number of daily meals and breakfast skipping, more sweetened beverages consumption, and low educational level of fathers.

IR is higher in urban than rural children and among Hispanics, American Indians, African Americans, East Asians, and South Asians than white European adolescents. However, it is increasingly observed across all racial boundaries, particularly with the increasing obesity rate. In a cross-sectional

Table 1 Various types of insulin resistance in children

IR type	Description
Partial IR	The impairment of insulin receptor expression is limited to specific tissue and consequently exhibits some features of insulin resistance according to the tissue affected
Complete IR	The impairment of insulin receptor expression is extensively distributed all over the body tissues and organs with the full expression of the syndrome
IR syndrome type A	It is a rare type of hereditary insulin resistance syndrome due to the lack of response of the tissues to the insulin. Patients with this syndrome are nonobese and demonstrate severe hyperinsulinemia, hyperandrogenism, and acanthosis nigricans. The clinical features are more severe in affected females than in males, and they mostly become apparent at the age of puberty
IR syndrome type B	It is a rare disorder caused by autoantibodies to the insulin receptor. This disorder is most frequently reported in middle-aged black women and is invariably associated with other autoimmune diseases
Compensated IR	The resulting hyperinsulinemia compensates for the body's metabolic needs and prevents metabolic derangement
Non-compensated IR	There is a progressive failure of compensatory hyperinsulinemia to fulfill the body's metabolic needs through puberty with rising blood glucose and triglyceride levels and metabolic derangement
Early childhood IR	Onset before the age of ten, a metabolic syndrome diagnosis cannot be made, but further measures should be taken if one of the parents has metabolic syndrome, DM type-II, dyslipidemia, cardiovascular risk factors, hypertension, or obesity
Late childhood IR	Onset after ten years of age, diagnosis of metabolic syndrome can be made
Social IR	It is a negative attitude directed towards avoiding or rejecting insulin therapy by some social groups

DM: Diabetes mellitus; IR: Insulin resistance.

study of urban Indian schoolchildren, Das *et al*[9] found that the overweight or obesity rates were 28.2%; about 21.8% of them had IR. Adolescence increases the risk of IR. Arslanian *et al*[10] showed that the IR rate was higher in obese adolescents than in obese adults, despite similar degrees of adiposity and glycaemic status. This observation could explain the relatively poor response of these obese children to metformin and the rapid decline of β-cell function observed in adolescents than in adults with diabetes mellitus (DM) type-II. IR shows marked variation among different races. Raygor *et al*[11] show that the overall IR was less in non-Hispanic Whites and African Americans than East Asians and South Asians. Ehtisham *et al*[12] also showed that South Asian adolescents have significantly more IR and body fat than white European adolescents, which may increase their risk of developing DM type-II. They attributed these racial differences to the ethnic differences in the composition of children's body fat. These racial differences are crucial to understanding the possible cardiovascular risk, specifically in high-risk races or ethnic groups.

PATHOGENESIS OF IR

IR is multifactorial.

PHYSIOLOGIC EFFECTS OF INSULIN

Insulin is a hormone produced from proinsulin in the beta cells of the pancreas when stimulated by elevated blood glucose. Proinsulin is broken apart, leaving insulin and C-peptide. Both are secreted and enter the bloodstream in equimolar amounts. Because insulin and C-peptide are equally secreted, both can be used to quantify endogenous insulin production. Average fasting serum C-peptide or insulin values are around 0-30 μIU/mL. The average daily insulin requirement is 0.5-0.7 units/kg of body weight[3]. Insulin stimulates the amino acids' entry into body cells. It enhances protein synthesis and fat storage and prevents fat mobilization for energy. It also promotes glucose entry into cells as an energy source. It has euglycemic effects by promoting glucose storage as glycogen in muscle and liver cells and inhibiting glucose production from liver or muscle glycogen from non-carbohydrates[13]. Insulin action starts by binding to a surface glycoprotein receptor expressed on the target cell's surface. This insulin receptor is composed of an alpha-subunit and a beta-subunit. Alpha unit binds the insulin, while beta-subunit is a tyrosine-specific protein kinase stimulated upon binding insulin to alpha subunit. This kinase activation generates a specific signal that ultimately results in insulin's effects on glucose, protein, and lipid metabolism. Insulin also mediates its growth-promoting effects by activating receptors linked to insulin-like growth factors[14]. IR does not necessarily involve all the insulin-dependent pathways

(partial IR). In partial IR, some manifestations such as hyperinsulinemia, hyperglycemia, hyperandrogenism, ovulatory dysfunction, soft tissue overgrowth, and acanthosis nigricans may present while the patients may have average lipid profiles[15,16].

GENETIC BASIS FOR IR

As many molecular pathways are concerned with energy homeostasis, protein and lipid metabolism, and insulin receptor functioning mechanism, many genetic mutations can end with IR development (Table 2). Insulin receptor mutations, mutations that stimulate autoantibody production against insulin receptors, or mutations that induce the formation of abnormal glucose transporter 4 (GLUT4) molecules or plasma cell membrane glycoprotein-1 molecules; all cause abnormal energy pathways and end with the development of IR. Mutations in the lipid pathway such as mutations in the adipocyte-derived hormones or their receptors (leptin, adiponectin, resistin), mutations in the peroxisomal proliferator-activated receptors (α, γ, δ), the mutation in the lipoprotein lipase gene, and other genes concerned with adipose tissue formation; all these mutations have a significant role in the development of IR. At the same time, mutations in proteases and serpin protease inhibitors cause IR and DM type II. The *CAPN10* gene is also engaged in GLUT4 vesicle translocation during the insulin-stimulated glucose uptake by adipocytes; it is also associated with IR and type 2 diabetes[17]. These mutations could occur in heterozygous or homozygous forms. The occurrence of several heterozygous mutations in the same person (a compound heterozygote) even when recessive; could have additive effects and produce significant consequences[18,19]. Insulin receptor pathway defects may occur due to mutations of the insulin receptor gene, causing a broad spectrum of inherited IRS, including type A syndrome of extreme IR, leprechaunism, Rabson-Mendenhall syndrome, and polymorphism in plasma cell membrane glycoprotein-1[20]. Insulin-like growth factor 1 (somatomedin C or IGF-1) is a hormone produced mainly by the liver, like insulin in the molecular structure, and plays a crucial role in childhood growth.

Growth hormone (GH) stimulates IGF-1 production[21]. Low IGF-1 levels are associated with many conventional cardiovascular risk factors related to increase IR. Kuang *et al*[22] found that obese prepubertal boys had lower IGF-1 standard deviation scores than boys without obesity and that whole-body insulin sensitivity index was positively correlated with IGF-1. Peroxisome proliferator-activated receptors (PPARs) are a group of ligand-activated transcription factors of the nuclear hormone receptor superfamily comprising of the following three subtypes: PPARα, PPARγ, and PPARβ/δ. Activation of PPAR-α reduces triglyceride levels and is involved in regulating energy homeostasis. Activation of PPAR-γ causes insulin sensitization and enhances glucose metabolism, whereas activation of PPAR-β/δ enhances fatty acids metabolism. Thus, the PPAR family of nuclear receptors plays a significant regulatory role in energy homeostasis and metabolic function. Mutations of this family induce IR[23,24].

ACQUIRED CAUSES OF IR

The parallel increase of IRS with the dramatic increase in the rate of obesity among children in the last few decades indicates the importance of environmental factors in increasing the rate of IR. Acquired causes of IR include lack of physical activity, exogenous obesity due to excess food intake, drugs, glucose toxicity due to hyperglycemia, increased free fatty acids, and the aging process. Puberty itself is occasionally associated with IR[25]. The development of polyclonal autoantibodies against insulin receptors preventing insulin from its action is a rare condition known as type B IRS, which should be distinguished from type A IRS[26]. IR may occur due to excess insulin antagonists in excessive steroid production such as Cushing syndrome, acromegaly, and stressful situations such as severe infection, trauma, surgery, uremia, diabetes ketoacidosis, and liver cirrhosis. Certain medications may also increase the risk of IR, such as glucocorticoid therapy, niacin, cyclosporine, and protease inhibitors[27]. Treatment with growth hormone can elicit transient IR. High sodium consumption causes hypertension, enhanced glucocorticoid production, and IR[28]. Protease inhibitor used as a part of anti-human immunodeficiency virus therapy is associated with lipodystrophy and IR. Nucleoside analogs, *e.g.*, acyclovir and abacavir, may also induce IR[29]. Insulin therapy can induce anti-insulin antibody formation, which is usually present in low titers in most patients. However, in rare cases, these antibodies can cause significant IR (pre-receptor or insulin-autoimmune syndrome) with enhanced insulin destruction at the subcutaneous injection site[30].

RISK FACTORS FOR IR

Alongside the genetic factors that play a fundamental role in the development of IR, other factors could have significant contributing effects. Babies born for mothers with DM, whether pregestational or gestational, are at risk for future development of impaired insulin sensitivity and obesity even when

Table 2 Various causes of the genetic type of insulin resistance

Site of defect	Type of defect	Clinical features
Insulin receptor: Mutations in the *INSR* gene (19p13.2) → faulty insulin receptor that cannot transmit signals properly	Type A IR syndrome mutation in the *INSR* gene (19p13.2)	Females are more affected than males. Appear during adolescence (delayed menses, 1ry amenorrhea, oligomenorrhea, hirsutism, acanthosis nigricans). Some males may have hypoglycemia & occasionally acanthosis nigricans. Later, they may develop DM
	Leprechaunism or Donohue syndrome (extremely rare) autosomal recessive	Extreme insulin resistance with fasting hypoglycemia and postprandial hyperglycemia, low birth weight, distinctive craniofacial features (bulging eyes, protuberant and low-set ears, thick lips, and upturned nostrils), skin abnormalities (hyperkeratosis), enlargement of the breast and clitoris in females and the penis in males, growth delays, & features of other endocrinopathies
	Rabson-Mendenhall syndrome (rare) autosomal recessive, also include Donohue syndrome	Severe insulin resistance, low birth weight, failure to thrive, lack of subcutaneous fat, muscle wasting, dental abnormalities; hirsutism, polycystic ovaries in females; enlargement of the nipples, genitalia, kidneys, heart, and other organs. Most affected individuals also have acanthosis nigricans, and distinctive facial features include prominent hypertelorism; a broad nose; and large, low-set ears
	Polymorphism in PC-1	It causes PC-1 overexpression to reduce autophosphorylation of the insulin receptor β-subunit, impairs insulin stimulation of insulin receptor activation & downstream signaling with short at birth, hyperinsulinemia, and high insulin resistance, high prevalence of diabetes, hypertension, and preeclampsia
Defects in fat cell and lipid homeostasis pathway	Congenital generalized lipodystrophy (mutations in *BSCL2* on 11q13, & *AGPAT2* gene on 9q34)	Autosomal recessive, extreme lack of body fat, and severe insulin resistance since birth
	Kobberling's syndrome (mutation in the *PPAR-δ* gene) FPL type 1	X-linked dominant, lethal in the hemizygous male. The autosomal dominant form of familial partial lipodystrophy was also described, characterized by the absence of subcutaneous fat, and presence of adipose tissue inside the body cavities and skeletal muscle hypertrophy. Fat loss is generally confined to the arms and legs. Fat loss is usually more prominent on the arms and legs' lower (distal) portions than proximal
	Dunnigan's syndrome (*LMNA* gene mutation) (1q22) FPL type 2	An X-linked dominant, lethal in hemizygous males, present with partial lipodystrophy characterized by sparing of the face. The onset of lipodystrophy usually occurs at or around puberty, with improper fat distribution (loss of fat in the limbs and gluteal region and variable regional fat accumulation on the face, neck, and axillary regions giving patients a cushingoid appearance). Females often have a more severe phenotype than males. An increased skeletal muscle volume and mass are also noted. Prominent veins (due to lipoatrophy) are noted in the limbs
	Allelic variation in PPAR-δ, PPAR-α, polymorphism of *UCP1*, *UCP2*, *UCP3* genes & polymorphism of β-2 and β-3 adrenergic receptor	Allelic variation in PPAR-δ influences body fat mass by effects on adipocyte; polymorphisms of *PPAR-α* gene can lead to higher triglyceride and insulin levels; polymorphism of the lipoprotein lipase gene was both linked and associated with insulin resistance; polymorphism of *UCP1*, *UCP2*, *UCP3* genes are associated with marked adiposity and DM type II; and polymorphism of β-2 and β-3 adrenergic receptors associated with chronic non-communicable disorders, such as cardiovascular diseases, asthma, chronic obstructive pulmonary disease, and obesity, as well as β-agonists and antagonists response and toxicity
Proteases CALP10	*CALP10* gene polymorphism	It is associated with reduced muscle mRNA levels and insulin resistance, metabolic syndrome, type II DM, and polycystic ovary syndrome
Other hormonal disorders	*POMC* mutations	Causes mutations in the *POMC* gene were linked with a clinical phenotype of adrenal insufficiency, red hair pigmentation, early-onset and rapidly progressive obesity, early-onset type 2 diabetes, hypothyroidism, hypogonadism, and growth hormone deficiency
	The *MC4R* gene mutations	MC4R mutations are the most common form of monogenic obesity and have been implicated in 1% to 6% of early-onset severe obesity
	The *MC3R* gene mutations	Inactivating mutations in the *MC3R* gene causes obesity in mice but is not clear in human
	Leptin and leptin receptor mutations	Homozygous leptin gene mutations are associated with the early onset of severe obesity and diverse impairment of physiological functions. Recessive leptin receptor mutations are associated with similar pathology in the homozygous state
	Ghrelin polymorphisms	Ghrelin is an orexigenic peptide that stimulates appetite and induces body weight gain and adipogenesis. Ghrelin polymorphisms may be associated with obesity and obesity-related phenotypes
	NPY gene	*NPY* gene polymorphism is associated with an increased risk of metabolic syndrome and its related phenotypes, such as central obesity and hyperglycemia
	CART polymorphisms	*CART* gene polymorphism is associated with a genetic predisposition to insulin resistance & obesity
	ER mutations	*ER* mutations cause impaired insulin sensitivity/glucose intolerance, hyperinsulinemia, and obesity
Prader-Willi syndrome	15q11.2–q12, uniparental maternal disomy	A key feature of Prader-Willi syndrome is a constant sense of hunger (hyperphagia) that usually begins at about 2 years of age with several physical, mental, and behavioral problems

Alström syndrome	Mutations in the *ALMS1* gene	The *ALMS1* gene provides instructions for making a protein whose function is unknown. *ALMS1* gene mutants in the hypothalamus might lead to hyperphagia followed by obesity and insulin resistance
Bardet-Biedl syndrome	Mutations in at least 14 different genes (often called *BBS* genes)	Vision loss is one of the significant features of Bardet-Biedl syndrome. Obesity is another characteristic feature of Bardet-Biedl syndrome. Abnormal weight gain typically begins in early childhood and continues to be an issue throughout life
Cohen syndrome	Mutations in the *VPS13B* gene (also called the *COH1* gene)	Cohen syndrome is an inherited disorder that affects many parts of the body and is characterized by developmental delay, intellectual disability, microcephaly, and weak muscle tone (hypotonia). Obesity develops in late childhood or adolescence
Biemond syndrome II		Biemond syndrome type II is a rare genetic neurological & developmental disorder reported in few patients with a poorly defined phenotype, including iris coloboma, short stature, obesity, hypogonadism, and postaxial polydactyly, and intellectual disability

DM: Diabetes mellitus; IR: Insulin resistance; PPAR: Peroxisome proliferator-activated receptor. UCP1, UCP2 and UCP3 are the uncoupling protein homologs.

they have an average birth weight[31]. The presence of hyperglycemia in pregnant mothers even without other signs of gestational diabetes is a mere risk factor for future IR and obesity in the offspring [32]. Children born to mothers with DM type I are more prone to have DM type II than children born with paternal DM type I[33]. Although many babies of mothers with gestational diabetes have excess body fat, the association of excess adiposity observed in these babies with the future development of IR is controversial[31]. The large birth size shows no association with later development of IR and impaired β-cell function in infancy. However, Huang *et al*[34] showed that the growth pattern during infancy could be related to the development of IR as decelerated infancy growth may be unfavorable to beta-cell function.

IR risk is high in newborns with small gestational age (SGA). However, studies showed that IR was not related to the birth weight but was related to the rate of weight gain during catch-up growth, especially in girls[34]. SGA may also result from IR's genetic causes as insulin is a potent antenatal growth hormone. Children born as SGA tend to have more intra-abdominal visceral fat than those with appropriate weight for age, even before the development of obesity. They are at more risk of having IRS in adolescence[35,36].

Consequently, SGA could be one of the manifestations of inherited IR with diminished fetal growth [37]. So, the relation between the birth weight and the risk of IR may follow a U-shaped relation[38]. Dabelea *et al*[39] showed that Pimas with low birthweight are thinner by 5-29 years. However, they are more insulin resistant and more liable to have DM type II than Pimas with average birth weight.

On the other hand, Pimas with high birth weight are more liable to be obese but less liable for IR regarding their body size[39]. Murtaugh *et al*[40] also observed similar findings. They showed a U-shaped relation between birth weight, body mass index (BMI), and fat mass in adolescents. So, children who rapidly gain weight are more liable to have IR, including preterm babies, during their rapid catch-up growth[41]. Ethnicity could pose a significant risk for IR as ethnicity and race affect glucose metabolism and insulin regulation. However, there are no international guidelines to address these racial/ethnic effects and recommend specific clinical advice[42]. Puberty is a physiological risk factor for IR due to various metabolic and hormonal changes. Insulin sensitivity drops by 25%-50% during puberty, reaching nadir by mid-puberty, then normalizes by the end of puberty. However, occasionally, puberty-induced IR does not resolve by the end of puberty, especially in adolescents who are obese, increasing the cardiometabolic risk of IR[43].

Deficiency of vitamin D is associated with many chronic conditions and diseases, including obesity, and increased metabolic dysregulation severity, such as IR and hyperlipidemia. Vitamin D performs a crucial role in the adipogenesis process and inflammatory condition in adipocytes and adipose tissue. Additionally, vitamin D can regulate adipocyte apoptosis and the gene expression responsible for the adipogenesis process, oxidative stress, inflammation, and metabolism in mature adipocytes. An adequate 1,25-dihydroxyvitamin D3 level is essential for normal insulin secretion[44,45]. Pires *et al*[46] showed that vitamin D deficiency in children with overweight or obesity increases the risk of IR during puberty.

Obesity is the most predominant pathophysiological risk factor of IR. IR positively correlated with the body mass index and proportion of body fat. Children with overweight or obesity have lower insulin sensitivity than children with average body weight[47]. The body fat distribution is also a significant risk factor that can predict IR. Although subcutaneous and visceral adipose tissues are related to IR, visceral adipose tissues more strongly correlate with IR than subcutaneous adipose[48]. Both subcutaneous and visceral adipose tissues secrete free fatty acids into the blood, correlated with the fatty mass. The higher the plasma-free fatty acid levels are, the more will be the IR. Visceral adipose tissues have more glucocorticoid receptors and elevated local glucocorticoids concentrations, which contribute to the development of metabolic screen[49]. In addition, visceral adipose tissues correlate with adiponectin levels, the degree of endothelial dysfunction and blood levels of C-reactive protein

(CRP), interleukin-6 (IL-6), and degree of systemic inflammation. In addition, ectopic non-visceral or subcutaneous fat deposition, such as intramyocellular fat in adolescents with obesity, is also associated with reduced peripheral insulin sensitivity[50].

Sex affects the impact of fat distribution on the development of fat resistance. In males, abdominal subcutaneous and visceral adipose tissues are associated with IR, while in females, visceral adipose tissues are associated with IR and insulin secretion. The lifestyles such as physical activity and nutritional behavior; have a poorly defined relationship with insulin sensitivity in the pediatric age[51]. However, increased caloric intake is a leading cause of obesity, IR, and hyperinsulinemia. A saturated fatty diet and sweetened beverages could be associated with altered insulin sensitivity and secretion. However, Weigensberg *et al*[52] showed that these changes were more observed in black but not white children, related to underlying ethnic differences. The consequence of lack of physical activity on IR, independent of weight changes and adiposity, remains debated. Marson *et al*[53] showed that exercise training, especially aerobic training, reduces the fasting insulin levels and IR indices in children and adolescents with obesity or overweight and may prevent the development of the MS and DM type II.

Some diseases make the child more susceptible to more increased risk of IR. Boys with Klinefelter syndrome may have truncal obesity, IR, and other features of MS as early as 4–12 years due to reduced physical activity[54]. In children with asthma and obesity or overweight, there is an increased risk of IR, which, together with obesity and MS, worsens lung function. These factors interact together, making asthma control more difficult[55]. Obstructive sleep apnea (OSA) is a common comorbidity in children with obesity. OSA induces sympathetic activation and enhances the development of IR[56]. In addition, the use of certain medications could increase the risk of IR. Systemic steroids used in managing various disorders commonly have significant adverse effects on body weight and insulin sensitivity[57]. Various psychotropic medications induce significant weight gain and IR, commonly observed soon after therapy [58].

CONSEQUENCES OF IR IN PEDIATRIC AGE

Most patients with IR do not develop DM type-II. However, IR is a crucial risk factor to develop DM Type-II in children. Two critical factors are needed to develop DM type-I: impaired β-cell function and IR[59]. The genetic basis of the patients determines the response of pancreatic β-cells to hyperinsulinism and IR. Children and adolescents with obesity and IR are more liable to impaired glucose tolerance than those with obesity but without IR[60]. However, Cali *et al*[61] showed that children with obesity who developed impaired glucose tolerance had a primary defect in β-cell function and insulin-resistant presence just served as an aggravating factor. The risk to develop DM type II can be predicted using the disposition index as IR alone is not enough to expect the risk of DM type II. This index measures the ability of the beta cell to secrete insulin in response to a glucose load.

Consequently, children with IR and hyperinsulinemia are at increasing cardiometabolic risk of developing MS in the different ethnic groups[62]. IR is associated with high levels of circulating endothelial dysfunction biomarkers (E-selectin and intercellular adhesion molecule) and decreased antiatherogenic adipocytokine adiponectin levels[63]. Children who have IR and hyperinsulinemia and did not develop type II DM are still at risk for other complications of IR such as dyslipidemia, early atherosclerosis, hypertension, progressive obesity (especially centripetal type), fatty liver infiltration, hypercoagulation, skin disorders such as acanthosis nigricans and increased skin tags, Polycystic ovary syndrome, renal impairment in the form of focal segmental glomerulosclerosis, and an increased risk of cancer[64]. Accordingly, IR should not be considered a benign condition even in the absence of DM type-II.

Although obesity (especially centripetal type) could lead to IR, genetically based IR may also provoke the progression of obesity. This finding explains why IR was observed in some non-obese lean sisters and brothers of obese children with IR, indicating IR was the primary disorder[65]. Genes accountable for IR could interact with various environmental factors (such as increased caloric and fat intake augmented with decreased physical activity), resulting in the development of IR, which increases secretory demand on β-cells, causing hyperinsulinemia[66]. Inulin serves as an anabolic hormone responsible for proper nutrient storage following meal ingestion. It also inhibits lipolysis, promotes fat storage, and consequently induces obesity[67]. Certain ethnicities are known to have very high circulating insulin levels, such as Pima Indians, Chinese children, and African American children have a higher prevalence of obesity[68-70]. However, this observation is unique for children and cannot be extended to adults.

Central obesity (with a high waist/hip ratio), a common IR finding, increases the risk for early atherosclerosis, premature coronary artery disease, stroke, and early death. Waist circumference strongly positively correlates with cardiovascular morbidity, BMI, and body fat percentage. The high risk of visceral obesity is due to increased free fatty acid efflux originating from the visceral fat, more glucocorticoid receptors, higher visceral fact concentrations of glucocorticoids, and the low leptin hormone levels with its protective effects compared to the subcutaneous fat[71-73]. As mentioned before, IR increases the risk of obesity, especially the centripetal type, and in turn, central obesity increases the risk of IR and

consequently increases cardiovascular risk. A population-based study by Ikezaki *et al*[74] showed that the reduced cardiovascular risk observed in the Japanese population compared to the American Caucasian population was linked to the considerable population variations in IR.

IR causes many metabolic changes, including hypertriglyceridemia, reduced serum protective high-density lipoproteins (HDL) cholesterol levels, increased atherogenic low-density lipoprotein (LDL) cholesterol particles, and low level of sex hormone-binding globulin (SHBG). Hence, it increases the atherogenic dyslipidemia status and the risk of early atherosclerosis[75]. Hyperinsulinemia also increases renal sodium retention augmented with the IR-induced sympathetic nervous system overactivity and fast vascular smooth muscle growth[76]. IR and hyperinsulinemia also induce early endothelial dysfunction preceding the formation of atherosclerotic plaques, starting the process of atherosclerosis during childhood[77]. These IR-induced changes may precipitate the development of early hypertension. Davis *et al*[78] showed that childhood and current cardiovascular risk factors especially total cholesterol in both males and females and BMI in females, are correlated with a higher carotid intimal-medial thickness in adulthood. In adulthood, coronary artery calcifications are also associated with high blood pressure and reduced protective HDL cholesterol levels measured during childhood. Lipid streaks can be found in the aortic wall in children as young as three years and in the carotid arteries by adolescence[79].

Fatty infiltration of the liver is a common problem observed in patients with IR, which could progress with time to end with inflammation (steatohepatitis), fatty liver fibrosis, and even liver cirrhosis and failure. With the increasing worldwide prevalence of obesity, the non-alcoholic fatty liver has become the most common pediatric liver disease. According to Schwimmer *et al*[80], the rate of fatty liver can reach up to 38% among children with obesity. Peng *et al*[81] showed that the prevalence of non-alcoholic steatohepatitis in children with obesity is strongly linked to high BMI-standard deviation score, gender, uric acid, waist circumference, body fat, IR, and hyperuricemia. Fatty liver infiltration is usually asymptomatic for many years. Still, it can be expected when liver enzymes rise, such as alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transferase, which may indicate hepatic fat accumulation. The aspartate aminotransferase/alanine aminotransferase ratio is generally less than one, but this ratio rises as fibrosis progresses[82]. It is commonly diagnosed as an incidentally by abdominal ultra-sound during an examination for other reasons[83]. Consequently, children with IR and obesity should be monitored to detect liver disease early.

IR and obesity commonly present with pseudo-endocrinal hyperfunction due to a decrease in hormonal binding proteins suggesting a common underlying controlling mechanism. Decreasing cortisol-binding globulin (CBG) causes an increase in free cortisol level, which causes the manifestations of Cushing's syndrome (pseudo Cushing's syndrome), which could overlap with the manifestation of MS. Fernandez-Real showed that the level of CBG is negatively correlated with insulin level[84]. Insulin-like growth factor-I binding protein (IGFBP-1) decreases in IR, causing an increase in free but not the total IGF-I. The increase in free IGF-1enhances the glucose-reducing effect of insulin, causing microvascular complications and manifestations of pseudo-acromegaly (acromegaloidism) with linear and acral growth (acromegaloid features) and signs suggestive of excess GH and normal levels of GH and total IGF-1[85]. IGFBP-1 Levels are negatively correlated with the severity of IR, while IGFBP-3 Levels correlate directly with hyperinsulinism[86]. Hyperinsulinemia also enhances linear growth by upgrading the skeletal IGF-1receptors, augmented by the increased free IGF-1 action. Pseudoacromegaly can also result from ghrelin gene polymorphism, which can induce obesity and IR[87].

IR also causes a reduction of thyroid-binding globulin plasma levels, confusing with the presence of hypothyroidism, and consequently, unnecessary treatment for hypothyroidism. In the presence of low TBG, we should consider other thyroid function tests, including thyroid-stimulating hormone and total and free thyroxine, and triiodothyronine. On the other hand, detecting hypothyroidism in IR and obesity is crucial. It could be the underlying cause of IR as thyroid hormones have a significant impact on glucose metabolism[88]. SHBG is a hepatic-produced protein that adheres to sex hormones with high specificity and affinity in males and females. SHBG is negatively correlated with fasting insulin levels and BMI. Sørensen *et al*[89] showed that puberty is associated with low SHBG levels, explaining the increased cardiovascular risk during puberty. They also showed that SHBG is a potent predictor of insulin sensitivity and metabolic risk during puberty. Chen *et al*[90] found that SHBG is a significant objective element of IR indices and can be used as an adequate positive indicator for IR in patients with polycystic ovary syndrome (PCOS), especially those who are overweight/obese. Reduced SHBG levels increase the free testosterone available to the tissues leading to manifestations of hyperandrogenism such as hirsutism and acne, even in the presence of normal total testosterone levels. Consequently, it induces progressive ovarian pathology, anovulation, and the characteristics features of PCOS[91].

The increased free androgens increase their aromatization and conversion into estrogens, increasing the incidence of adipo/gynecomastia in male adolescents with more GH production and increasing longitudinal bone growth[92]. Littlejohn *et al*[93] described a series of four girls with severe IR, which showed nearly all the features of pseudo-endocrine hyperfunctions associated with IR. The girls had severe prepubertal obesity due to severe IR, followed by the appearance of early childhood pseudo Cushing's syndrome, then manifestations of pseudo-acromegaly, which herald adolescent polycystic ovary syndrome.

People with overweight or obesity commonly have vitamin D deficiency even in different age groups and ethnicity. As vitamin D is fat-soluble, and there is a marked increase in fat mass in patients with obesity, there is a volumetric dilution causing a relative deficiency. Consequently, people with obesity need higher supplemented doses to maintain normal serum levels of 25-hydroxyvitamin D than people with average weight[94]. Lind *et al*[95] showed that serum levels of 25-OH-vitamin D are negatively correlated with fasting insulin and positively correlated with insulin sensitivity. They also showed that IR is associated with low 25-hydroxyvitamin D3 levels. Vitamin D is essential for the normal secretion of insulin.

Consequently, vitamin D deficiency aggravates the metabolic derangement in IR and obesity. Vitamin D binding protein (VDBP) binds to about 90% of the total vitamin D while only 1% of vitamin D metabolites is present in a free unbound form. VDBP is a macrophage-activating factor with a potent tumor growth inhibitor and strong anticancer activity. Ashraf *et al*[96] showed that VDBP levels are inversely correlated with IR and hyperinsulinemia. Consequently, low vitamin D status is associated with higher risks of several cancers in patients with obesity[97]. Meanwhile, Pratley *et al*[98] showed that VDBP polymorphism is connected to the increased risk of diabetes in Pima Indians.

IR-related obesity characterizes by increased markers of inflammation like CRP and erythrocyte sedimentation rates. The inflammation is more common in girls than boys who have BMI more than 95th percentile[99]. CRP levels correlate significantly with BMI and adipose tissue mass in the young adult population[100]. The visceral obesity, systemic inflammation, and cellular dysfunction associated with IR are significant cardiovascular risk factors. When started in childhood and persist until adulthood, it induces various chronic cardiovascular diseases such as atherosclerosis, systemic hypertension, and coronary artery diseases[101]. However, CRP elevation and degree of inflammation could improve with dietary modification and more grain consumption[102]. As asthma and obesity are associated with systemic inflammation, increased pro-inflammatory state, and the effects of increased leptin levels on Th1 cytokine responses, there is an increase in asthma prevalence among children with obesity, especially during puberty[103]. Castro-Rodríguez *et al*[104] showed that BMI positively correlates with the prevalence of asthma in both boys and girls. They also showed that girls who become overweight or obese between 6 and 11 years are seven times more likely to have asthma at age 11 or 13. Consequently, weight reduction helps to improve pulmonary functions and asthma symptoms and reduce the need to use rescue bronchodilators and the frequency of asthma exacerbations[105]. Obstructive sleep apnea, a common complication of obesity, can increase IR. IR is expected to present when children with obesity have obstructive apnea-hypopnea index ≥ 4.9[106].

High insulin levels in IR stimulate insulin and IGF-1 receptors in human keratinocytes, causing the increased thickness of the stratum corneum with hyperpigmentation in a racially dependent manner (Acanthosis Nigricans). The posterior region of the neck, axillae, antecubital fossae and groins are the most common affected sites. In contrast, other flexural areas, sub-mammary region, umbilicus, elbows, knuckles, and, in extreme cases, the entire skin are less commonly involved. The degree of IR and the insulin blood levels positively correlate with the severity of acanthosis nigricans[107-109]. Özalp Kızılay *et al*[110] showed that IR is more predictive of psychiatric illness than obesity-related metabolic comorbidities. Consequently, it is crucial to assess the presence of psychiatric malfunctioning in obese children, particularly those with IR. We highly recommend routine screening to identify the presence of psychiatric disorders in children with obesity.

CLINICAL PRESENTATION

Appropriate history and comprehensive clinical examination provide a lot of information that helps to diagnose IR.

PATIENT MEDICAL HISTORY

IRS is commonly associated with dyslipidemia, obesity, skin changes, atherosclerosis, hypertension, DM type-II, hyperandrogenism, and polycystic ovarian syndrome. The clinical presentation of IR is variable and depends on its etiology and severity. History can elaborate on the presence of high-risk IR. Maternal history of gestational DM, preeclampsia, or intrauterine growth restriction could expect the development of IR, especially in obese offspring. The large or small birth weight for gestational age is also a significant risk factor for IR. Microcephaly, with head circumference less than the 10th centile at birth, may indicate significant intrauterine growth retardation, which could be a sign of genetic causes of IR, or the growth restriction itself could induce IR[111,112]. It is critical to evaluate preceding anthropometric measurements using appropriate growth charts and give attention to the catch-up growth in smaller babies. Particular attention should be given to recent rapid weight gain, specifically if be associated with dysmorphic features. History of cold intolerance, easy bruising, generalized weakness, and easy fatigability could indicate the presence of other endocrine disorders such as hypothyroidism or Cushing's syndrome[113].

The onset and duration of obesity are also crucial to predict IR's presence and complications. Infants and children who developed obesity and significant weight gain before the age of five and particularly in the 1st year of life are more liable to have genetic causes for IR and obesity. Early development and a longer duration of obesity predict an adverse metabolic profile of the affected child[114]. However, all children with overweight or obesity have IR, and not all children with IR are overweight or obese[115]. The dietary history is also essential considering the overall caloric intake, considering the food elements that significantly impact the weight gain and the metabolic pattern in the child with overweight or obesity. Taking a good dietary history is mandatory to identify the dietary components that could lead to obesity development and, at the same time, can give a clue to improve the metabolic derangement even without significant weight loss[116]. At the same time, the sleeping pattern is equally essential to dietary history. The duration of the sleep, the sleep pattern, and the presence of sleeping disorders should be addressed. OSA is a frequent disorder observed in children with obesity, which further increases IR due to various pathologic mechanisms such as tissue hypoxia and sympathetic activation [56]. Therefore, children with obesity and snore, mainly when mouth breathing, should be screened for the presence of OSA with polysomnography[117].

Good medical history should address the lifestyle, sedentary behavior, and the child's physical activity. With the overuse of the media, especially during the current coronavirus disease 2019 pandemic and spending more and more media time, including television, online teaching, computer gaming, and smartphone use, we expect a significant rise in the rate of obesity and consequently IR [118]. However, any physical activity, even non-weight reducing activity, may provide a beneficial metabolic effect on the body fat composition and improve the general body insulin sensitivity. Therefore, any degree of physical activity should be encouraged[119]. As many medications significantly impact insulin sensitivity, a medication history is mandatory while managing a child with either obesity or suspected IR[120]. We should ask about any medications/drugs that affect appetite, glucose, or lipid metabolism. As mentioned before, some psychotropic medications such as Clozapine, Olanzapine, and Risperidone, corticosteroids, growth hormone therapy, some antihypertensive drugs such as beta-blockers, and diuretics as thiazides, antiepileptics as Valproate, and some common antineoplastic drugs as Tacrolimus, Cyclosporine A, and Sirolimus[121]. As IR has many genetic causes, positive family history of similar conditions, obesity, DM type II, or other forms of metabolic disorder is common.

PHYSICAL EXAMINATION

Adequate physical examination is mandatory as it helps assess the presence and the severity of IR and the underlying cause. General appearance can hint about the underlying lesion, especially in the presence of dysmorphic features and pseudo-acromegalic features (with suppressed GH levels), which could signify the presence of genetic or secondary causes of IR. The anthropometric examination is essential during any child examination, particularly when overweight or obese, is expected. Weight, height, BMI, mid-arm, and waist circumference should be measured and plotted on the appropriate charts and growth curves. Height is measured to the nearest 0.5 cm, while the body mass is measured to the nearest 0.1 kg using a standard stadiometer. The waist circumference is measured using a cloth tape at the end of normal expiration to the nearest 0.1 cm at the midpoint between the uppermost lateral border of the right iliac crest and the lowest rib. Children are considered overweight when their BMIs are higher than the 85th percentile for age and sex, or BMI equals to or more than 25 kg/m^2. They are considered obese with BMIs higher than the 95th percentile or BMI equal to or more than 30 kg/m^2[122]. However, not all children with obesity have IR, but most children with BMIs more than 35-40 kg/m^2 have IR[123]. Fat distribution, especially the abdominal fat, impacts the development of IR and consequent non-alcoholic fatty liver disease in obese children. So, we should evaluate the intraabdominal type (apple-shaped) *vs* peripheral fat (gluteal-femoral, extremity, or pear-shaped) and document waist circumference and waist/hip ratio. The body fat percentage can be assessed using different methods, such as an X-scan bioelectrical body composition analyzer[124]. Tall stature may indicate the presence of underlying endocrine or chromosomal disorders, *e.g.*, Klinefelter syndrome.

The blood pressure is measured using an appropriately sized cuff after at least 5 min of rest, preferably with an automated instrument in a seated position. At least two readings are measured, and the average value is used for analyses and adjusted for age, sex, and height. Occasionally, we may need a 24-h ambulatory blood pressure evaluation. Blood pressure could be high in some endocrine disorders that may induce IR, such as Cushing syndrome. Giordano *et al*[125] found an association between a decrease in nocturnal blood pressure and insulin levels (as a measure of IR), regardless of obesity or diurnal blood pressure levels. The pulse also should be evaluated for any resting tachycardia. Flanagan *et al*[126] found that the insulin sensitivity in the young adult correlated with cardiac sympathovagal balance in males but not in females, suggesting the effect of gender on the autonomic modulation of IR. We should also search for signs of heart failure to rule out obesity-induced cardiomyopathy[127]. The examiner should also ask about any signs of respiratory distress (for underlying bronchial asthma), expiratory wheezing, and snoring, indicating upper airway obstruction and possible OSA.

Abdominal examination is a crucial part of child examination for IR. Abdominal obesity is diagnosed when waist circumference equals to/more than 90th percentile for age and gender. After adjusting for BMI percentile, waist circumference significantly correlates with total and abdominal visceral fat and insulin sensitivity. Some studies revealed that BMI and waist circumference together are superior predictors of metabolic risk than only one of them[128,129]. It is also essential to look for striae and detect organomegaly. Hepatomegaly may present as a sign of congestive heart failure due to obesity-induced cardiomyopathy or steatosis and non-alcoholic steatohepatitis[130]. Abdominal pain could occur as a side effect of metformin treatment.

Skin is commonly affected by IR. Obesity, IR, or DM indicators may include hypo/hyperpigmentation, acanthosis nigricans, abdominal skin striae, skin tags, fatty breast (adipomastia) in males, hirsutism, acne, frontal balding, and signs of virilization in females. Higher insulin levels could associate with premature pubarche. Premature pubarche and virilization in girls are potential antecedents of PCOS. It is due to increased insulin levels with a causal relationship between high insulin levels and hypersecretion of the adrenal and/or ovarian androgens[131]. Acanthosis nigricans is a darkly pigmented, velvety, hyperkeratotic, papillomatous skin lesions in body folds such as the skin of the neck or axilla. The presence of acanthosis nigricans is due to acanthocytes' exposure to hyperinsulinemia, interacting with insulin-like growth factor-1 receptors on these cells[132,133]. Multiple skin tags are more sensitive than acanthosis nigricans in identifying abnormal glucose/insulin metabolism. Multiple skin tags should increase suspicion of increased risk of IR or hyperinsulinemia[134]. Examinations of the extremities for strain and deformities should be done as genu varum and other lower extremity postural defects are common in children with overweight or obesity[135].

LABORATORY DIAGNOSIS OF IR IN CHILDREN

Diagnostic standards for IR in children are not yet established due to various causes, including different techniques to measure IR, insufficient patient size, and lack of adequate longitudinal long-term pediatric studies. Thorough evaluation of impaired sensitivity and responsiveness to the insulin thus needs an assessment of insulin dose-response curves. Hyperinsulinemia is defined when the fasting insulin level is > 15 μU/mL, or peak insulin level is > 150 μU/mL or > 75 μU/mL at 2 h after the oral glucose tolerance test, which may indicate IR[17].

DIRECT MEASURES OF INSULIN SENSITIVITY

Direct measures of insulin sensitivity are valid and reliable for the measurement of insulin sensitivity. They include the hyperinsulinemia euglycemic glucose clamp (HEGC) and the insulin-suppression test (IST). These tests are time-consuming require intravenous infusions and frequent sampling. It is troublesome for participants, is expensive, and needs a research setting.

The HEGC is the gold standard to assess IR. However, the frequently sampled intravenous glucose tolerance test (FSIVGTT), and oral glucose tolerance test (OGTT) are also valid and often used methods as they are more simple and more accessible to be used[16]. In HEGC, the insulin is infused intravenously after overnight fasting at a constant rate (5-120 mU/m^2/min), increasing and maintaining a steady state of systemic insulinemia, which induces increased glucose uptake by the peripheral tissues and suppresses the hepatic glucose production, causing hypoglycemia. Consequently, a bedside glucose analyzer regularly monitors blood glucose levels at 5-10 min. An intravenous glucose 20% infusion at variable rates occurs to maintain (clamp) glucose levels within the normal range to maintain a euglycemic state. The glucose infusion rate is adjusted and directly proportional to insulin sensitivity to maintain the euglycemic state. The more glucose is needed to maintain the euglycemic state, the more the body is sensitive to the insulin effect. We need less glucose infusion to maintain the euglycemic state in IR. Caution should be taken to avoid insulin-induced hypokalaemia, and potassium phosphate infusion should be given to prevent hypokalaemia[136]. This test has the advantage of directly measuring the whole-body tissues' glucose disposal at a certain level of insulinemia but has the disadvantage of technical difficulties[137].

The IST also directly evaluates metabolic insulin sensitivity/resistance to the exogenous insulin after suppressing endogenous insulin production. First, we suppress the endogenous secretion of insulin and glucagon by giving intravenous infusion somatostatin (250 μg/h) or octreotide (25 μg bolus, followed by 0.5 μg/min) after overnight fasting. At the same time, we infuse both insulin (25 mU/m^2/min) and glucose (240 mg/m^2/min) in the same vein. We continuously monitor glucose and insulin from the contralateral arm every 30 min for 150 min, after that, every ten minutes till the end of the third hour. We usually reach the steady-state plasma insulin and steady-state plasma glucose (SSPG) between 150-180 min of the test. We evaluate the sensitivity of the tissue to the exogenous insulin by measuring SSPG levels. The higher the SSPG levels are, the lower the tissue sensitivity to the insulin is, and the lower the SSPG levels are, the higher the insulin sensitivity is[138]. This test provides a highly reproducible direct measure of metabolic actions of insulin and is less technical dependant than HEGC. However, applying

IST in the clinical setting is not practical[139].

INDIRECT MEASURES OF INSULIN SENSITIVITY

Minimal model analysis of FSIVGTT provides an indirect estimate of metabolic insulin sensitivity/resistance, acute insulin response, and disposition indexes. After an overnight fast, we inject a bolus of glucose (0.3 g/kg body weight) by intravenous infusion over 2 min starting at time 0; we collect serial blood samples for glucose and insulin level until three hours after the test. The test assesses insulin sensitivity/resistance by a computed mathematical assessment of glucose and insulin dynamics. It examines the plasma glucose dynamics and the glucose per se to promote its disposal and suppress the hepatic glucose production without an increased insulin effect. It is easier than the glucose clamp method[140].

OGTT is an easy, simple test commonly used in clinical practice, especially during early pregnancy, to diagnose glucose intolerance and type 2 diabetes. However, it tests the glucose tolerance and the ability of the body to dispose of the orally ingested glucose and not IR. We give a standard 75 g of glucose orally after an overnight fast. Then blood samples to determine glucose and insulin levels are taken at 0, 30, 60, and 120 min[141]. OGTT provides the benefits of having fewer blood samples with high correlations with the euglycemic hyperinsulinemic clamp in adult studies but not well studied in the pediatric age[142].

SIMPLE SURROGATE INSULIN SENSITIVITY/RESISTANCE INDEXES

These indexes were created to simplify the measurement of insulin sensitivity. They depend on estimating the fasting blood glucose and insulin levels after overnight fasting. Fasting induces a steady basal state where insulin and glucose plasma levels should be maintained in the normal ranges in a healthy human. So, these indexes reflect the basal insulin secretion by pancreatic β cells and the hepatic insulin sensitivity/resistance. These indexes use a specific mathematical formula that corrects the individual variabilities in glucose and insulin secretion and clearance. However, these indexes are insensitive, lack standardization, and cannot define universal cut-off points for IR[143]. The most common indexes used are the homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI), insulin sensitivity index, ISI (0, 120), and adipose tissue IR index (Adipo-IR).

HOMA assumes a feedback loop between pancreatic β-cell and liver. This means that pancreatic β-cell is stimulated by glucose to secrete insulin which in turn stimulates the glucose uptake by the liver and inhibits hepatic glucose production (HGP). In IR, there will be suppression of the HGP. HOMA score is calculated from the following formula: [Fasting glucose (mg/dL) × Fasting insulin (μU/mL)]/405.

An important limitation of the HOMA score is that it indicates the fasting steady-state of pancreatic β-cell and not the actual dynamic state of β-cell Insulin secretion. There is insufficient evidence to support HOMA cut-off values frequently used to identify IR in pediatric studies[144].

QUICKI is also derived from fasting blood glucose and plasma levels. It provides a consistent, reproducible, and precise insulin sensitivity index with outstanding positive predictive value. It uses the following formula: 1/[log of fasting insulin (μU/mL) + log of fasting glucose (mg/dL)].

Adding the log of fasting glucose to the log of fasting insulin provides a reasonable correction and better linear correlation with insulin sensitivity by the HEGC method both in diabetic and non-diabetic patients. It is an appropriate and practical test. It can be used in extensive epidemiological or clinical research studies and help follow changes after therapeutic interventions[145]. ISI (0, 120) is developed by Gutt *et al*[146] and uses the insulin and glucose concentrations both fasting (0 min) and at 120 min post- OGTT. It can screen both obesity and glucose intolerance and correlate well with the euglycemic hyperinsulinemic clamp.

Consequently, it is superior to other indices of insulin sensitivity, such as the HOMA formulae[146]. Adipo-IR is obtained by measuring the fasting level of FFA and insulin. Adipo-IR is well correlated with adipose tissue insulin sensitivity. Adipo-IR is well correlated with and a significant predictor of MS. However, its predictive value is affected by age and physical fitness[147].

IR SCREENING

There is no rationale for screening children for IR, even among children with obesity. Considering that IR in children with obesity increases cardiovascular risks, screening for IR is valid. However, any screening program needs accurate, reliable, easy, and reproducible tests. Screening tests for IR also need to be adjusted for ethnic groups, genders, and pubertal stages. Using lengthy and costly methods such as HEGC or IST is impractical. At the same time, tests that depend on fasting insulin as a screening test are unreliable measures of insulin sensitivity[148].

Meanwhile, there is no definitive recommended pharmacological therapy for isolated IR. Accordingly, it will be wiser to screen and actively manage children with obesity rather than screening for IR[149]. Among the tools that can screen for obesity and IR is ISI (0, 120). It has good predictive value for obesity, IR, DM, and cardiovascular disease (CVD) events. However, it needs more evaluation, particularly in the pediatric age. Rutter *et al*[150] showed that ISI (0, 120) and the MS, not the HOMA-IR index, could independently predict CVD. They also showed that MS might not catch all the CVD risks related to IR. Moreover, Adipo-IR may serve as a useful screening tool to detect IR, especially in those with a high risk of developing DM type-II, even in the absence of clinical risk factors such as obesity or impaired glycemia[25].

PREVENTION OF IR

To prevent future IR, we should target all the factors that could help the development of IR in the future, such as factors that affect fetal growth and development as maternal obesity, pregestational and gestational DM, maternal smoking, especially during pregnancy, maternal undernutrition, and premature delivery[2]. Exclusive breastfeeding until at least four months and continuing until the age of two has a significant impact on reducing child obesity and IR in the future[151,152]. However, there are no sufficient data about the direct effect of breastfeeding in IR prevention. However, its role in obesity prevention is solid. The pancreatic β cells differentiate during fetal life. Still, their maturation and ability to secrete insulin in response to glucose stimulation are modulated during the early postnatal life and modified by the weaning practice[153]. Consequently, proper weaning timing and technique are essential contributors to preventing childhood obesity and IR[154,155]. As antibiotic treatment early in life could increase the risk of obesity, co-administering prebiotic with antibiotics could reduce obesity risk, as demonstrated by Klancic *et al*[156].

Obesity is strongly linked to IR either with a cause-result effect, dietary interventions to prevent obesity could help reduce the prevalence and severity of IR. Increased intake of saturated fat is associated with diminished insulin sensitivity in children. However, we may notice some ethnic differences between children[52]. On the other hand, the intake of a healthy diet low in saturated fat and cholesterol starting at the age of 7 mo is associated with a positive impact on IR at the age of nine[157]. Van Hulst *et al*[158] also showed that reducing saturated fat and raising fruit and vegetable intakes during childhood may enhance insulin sensitivity during puberty. Improving physical fitness in toddlers, preschool, and school children, especially those at high risk for obesity, is an effective preventive way to prevent obesity and IR. Even when not associated with weight reduction, physical activity prevents and even improves IR[159].

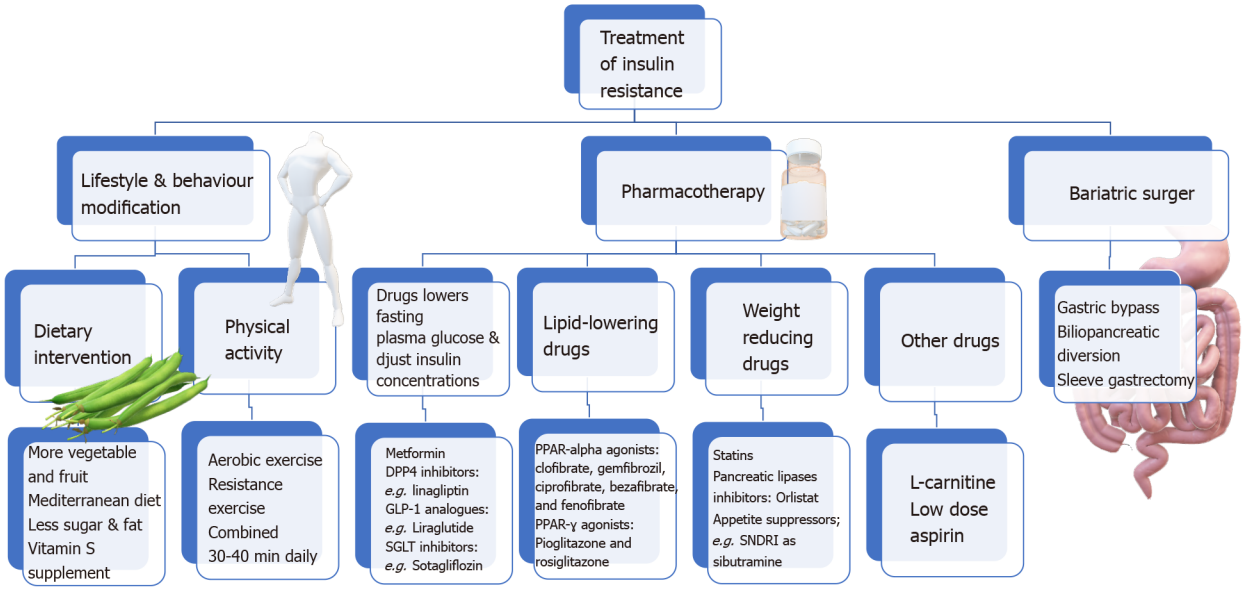
TREATMENT OF IR IN CHILDREN

The main aim of the treatment of IR in children is to prevent the progression of compensated IR to decompensated IR, enhance insulin sensitivity, and treat possible complications. There are three main lines for treatment: Lifestyle and behavior modification, pharmacotherapy, and surgery (Figure 1).

Lifestyle and behavior modification

Lifestyle and behaviour modification is the cornerstone in IR prevention and management. It includes dietary intervention and increasing physical fitness and activity. Exercise may have the upper hand and a more substantial impact in improving insulin sensitivity than the isolated weight reduction[160]. There is a direct relationship between the daily step number the subject does with the blood level of IGF-1 and an inverse relation with high sensitivity CRP. So, physical activity can modulate IR and related inflammation, whereas sedentary time affects fatty acid-binding proteins[161]. Despite the apparent benefits of physical fitness on insulin sensitivity, the exact mechanism is unclear, mainly that improvement in insulin sensitivity occurs earlier than or even without actual loss of body weight[162]. There are not enough studies to compare the different degrees of exercise intensities or the effects of single-session exercise *vs* a training regimen on insulin sensitivity. Also, there is no strong evidence about the optimal exercise form that produces maximum effects on insulin sensitivity. However, a combination of aerobic and resistance exercise training regimens improves insulin sensitivity[163]. Children with IR should be aggressively involved in an exercise program, such as swimming or walking for 30-40 min for most weekdays to provoke glucose entry into the muscles without insulin involvement. Pedometers can be used to monitor their physical activities. Continuation of physical exercise is of utmost importance as cessation of exercise after initial improvement of insulin sensitivity is associated with reverting to the pre-exercise levels (a condition known as rebound phenomenon with higher IR)[164].

Dietary intervention



DOI: 10.4239/wjd.v13.i4.282

Figure 1 Different lines for management of insulin resistance. DPP4: Dipeptidyl peptidase-4 inhibitors; GLP-1: Glucagon-like peptide-1; PPAR: Peroxisome proliferator-activated receptor; SNDRI: Serotonin-norepinephrine-dopamine reuptake inhibitor.

Dietary intervention improves insulin sensitivity in children and adolescents through weight reduction and other unknown mechanisms. Avoiding increasing dietary fat intake, reducing saturated fat intake, increasing unsaturated fat (*e.g.*, olive oil and other vegetable oils) intake, increasing vegetable and fruit consumption, and reducing sugar intake are the main elements for the dietary intervention to improve insulin sensitivity[101]. Adherence to the Mediterranean diet, which incorporates vegetables and olive oil, avoiding the intake of highly processed food and sugar-sweetened beverages, helps to reduce the body weight and improve insulin sensitivity[165-167]. As mentioned before, intake of a high whole-grain diet or dietary fibres improves insulin sensitivity and help to reduce the body weight and BMI in children, adolescents, and adults[168,169]. Probiotic supplementation showed significant improvement in IR indicators in animal studies. It improves inflammatory and oxidative markers, lipid profile, short-chain fatty acids production and microbiota structure. These changes could result from strengthening the intestinal barrier and enhancing the immune system and metabolism. Consequently, adding probiotics to a healthy diet and changing the lifestyle to be more active with/without medications could help to attenuate IR[170,171]. Meanwhile, vitamin D supplementation positively improves insulin sensitivity and cardiovascular and metabolic risk factors in children with obesity[172].

PHARMACOLOGIC MANAGEMENT

There is no specific pharmacologic management for IR. However, pharmacologic treatment is occasionally needed to augment lifestyle management, especially in significant childhood obesity. Because of the severe side effects that could rarely happen, pharmacologic therapy should be sued only in selected cases. We should consider the patient's age, BMI, and associated comorbidities when considering pharmacotherapy. Close monitoring is also required as long-term effects still need more studies[173,174]. Pharmacotherapy involves two main categories: Drugs that decrease fasting plasma glucose and adjust insulin concentrations, lipid-lowering drugs, and drugs that enhance weight loss.

Drugs that decrease fasting plasma glucose and adjust insulin concentrations

The Biguanide-derived metformin is the drug of choice in treating DM type-II in children above ten years. It also showed documented efficacy in improving IR through reducing the body weight, BMI, fasting plasma glucose, and insulin levels. It enhances insulin binding to its receptor even in the presence of receptor autoantibodies (IRS type B) through phosphorylation augmentation and increasing insulin receptor-tyrosine kinase activity[175]. It increases the peripheral tissues glucose utilization by enhancing phosphoinositol 3-kinase at the receptor level, potentiating glucose transporters GLUT1 and GLUT4 isoforms translocation to the cell membrane of various tissues[17]. It is also effective even in the presence of insulin receptor mutation[17]. Recent studies also showed that pre-prandial metformin could acutely reduce blood glucose levels *via* intestinal glucose transport inhibition and increase intestinal glucagon-like peptide-1[176]. It also reduces the food intake with a further reduction of the

body weight, fasting glucose, glycated hemoglobin (HbA1c), insulin, and cholesterol levels. These effects help to improve BMI, body fat composition, lipid profile, and consequently IR. However, although metformin improves insulin sensitivity, it is not indicated in cases with isolated IR[177]. According to the 2017 guidelines endorsed by The Pediatric Society, metformin should be used in selected pediatric patients such as girls with obesity, polycystic ovaries, and glucose intolerance[178]. When using metformin, gradually increased doses can minimize the various gastrointestinal side-effects. Vitamin B12 deficiency could result especially with the long-term use of Metformin, and close monitoring may be required[2].

Incretins are a group of gut-derived metabolic peptide hormones that are promptly secreted in reaction to a meal and promote the reduction of blood glucose levels by augmenting insulin secretion from pancreatic β-cells and inhibiting glucagon release from the alpha cells, a blood glucose-dependent mechanism. There are two main categories of incretins: the intestinal glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide known as gastric inhibitory peptide. Incretins are rapidly deactivated by the enzyme dipeptidyl peptidase-4 (DPP-4)[179]. DPP4 inhibitors such as linagliptin are relatively newly discovered glucose-reducing drugs which antagonize the inhibitory effects of endogenous incretins on insulin secretion, causing increasing insulin secretion in response to blood glucose levels. DPP4 inhibitors improve fasting and post-prandial blood glucose and HbA1c levels[180]. Linagliptin also has protective effects against diabetes-induced macrovascular and microvascular complications. However, Linagliptin is still an investigational drug that has not yet been approved in children and adolescents due to insufficient clinical studies[181].

GLP-1 also reduces the inflammatory cytokine release, inhibits macrophage infiltration into the fatty tissue, the liver, and the vascular wall, and reduces IR-induced chronic inflammation[182]. GLP-1 inhibits food intake through actions in the hypothalamus, including the paraventricular nucleus[183]. Consequently, GLP-1 analogs, such as Liraglutide, could enhance insulin sensitivity and reduce body weight in patients with IR. Danne *et al*[184] showed that Liraglutide use in adolescents with obesity has a safety and tolerability profile like that observed in adults.

Sodium-glucose cotransporters (SGLT) are a group of glucose transporter responsible for apical sodium and glucose transport across cell membranes. They are responsible for the absorption of glucose and galactose in the gastrointestinal tract (SGLT1) and reabsorption of 90% of filtered glucose in proximal renal tubules (SGLT2)[185]. Sotagliflozin (an oral potent dual SGLT1 and SGLT2 inhibitor) effectively improves the glycaemic state by reducing HbA1c, post-prandial blood glucose, body weight in adults with DM type-I and type-II[186]. An animal study showed that the selective SGLT2 inhibitor Empagliflozin was effective as monotherapy or when combined with DPP-4 inhibitor in improving IR in mice with proper glycaemic control[187]. However, we need more consistent data to determine its actual benefits and adverse effects on adults and children with IR.

Lipid-lowering drugs

The PPAR agonists regulate energy (glucose and lipid) metabolism, inflammation, and cell proliferation. They are of three groups: alpha, beta/gamma, and delta used to treat symptoms of MS, primarily by reducing triglycerides and blood sugar[188]. PPARα agonists are the main target of fibrate drugs (clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate). They decrease triglyceride levels *via* PPARα transcription factor, mainly in the liver, inducing fatty acids oxidation, and controlling gluconeogenesis and amino acid metabolism. They are primarily indicated in cholesterol disorders and hypertriglyceridemia[189]. They can also reduce the inflammatory markers such as fibrinogen, CRP, plasminogen activator inhibitor-1, IL-6, and vascular cell adhesion molecule-1 expression[190]. When combined with statins, care should be taken as they may induce a severe form of rhabdomyolysis. Children with severe hypertriglyceridemia (> 400 mg%) can use fibrates to prevent pancreatitis with high tolerability[191]. The PPAR-γ agonists are ligand-activated transcription factors that treat DM and other diseases with IR[192]. PPAR-γ agonists (*e.g.*, pioglitazone and rosiglitazone) can decrease adhesion molecules and inflammatory proteins. They also have lipid-lowering effects through enhancing lipid oxidation, reducing adipocytes' free fatty acid secretion, decreasing intramyocellular lipids, and improving muscular IR. They also decrease 11 beta-hydroxysteroid dehydrogenase type 1 and testosterone levels in IR females[193,194]. Animal studies showed a possible role of PPAR-γ agonists in improving pulmonary inflammation, especially that present in asthma[195].

Weight reducing drugs

Weight reduction by 5%-7% is enough to decrease the diabetes risk by 58% in high-risk persons. Statins are commonly used drugs to reduce body weight. Orlistat is a potent inhibitor of gastric and pancreatic lipase enzymes, y reducing the absorption of cholesterol and triglyceride from the gastrointestinal tract. Orlistat improved lipid profile and led to faster glycaemic control and IR parameters. It also improves retinol-binding protein-4 (RBP-4) and visfatin. RBP-4 is known to be associated with an increased cardiovascular risk. Visfatin is a novel adipokine known to have neuroprotective effects against cerebral ischemic injury[196]. Orlistat can enhance insulin sensitivity in children and adolescents. However, it should be used wisely and in selected cases in this age group[197,198]. Sibutramine is a weight-reducing drug used to treat obesity mainly by its appetite-suppressing effect. Care and awareness about the loss of its effectiveness and the possible detrimental adverse effects should be given[199]. Statins reduce

hepatic cholesterol synthesis by inhibiting the 3-hydroxy-3-methylglutaryl-CoA reductase enzyme, consequently increasing the hepatocyte uptake of LDL decreases the atherosclerosis progression. Even though statins are safe and well-tolerated in children, their long-term safety is not firmly established in this age group[200].

Other drugs

L-carnitine has been used for several years as adjuvant therapy in oxidative stress. A meta-analysis by Xu *et al*[201] showed that L-carnitine is beneficial and effective in treating patients with IR. Children with severe dyslipidemia and IR with a high risk for pancreatitis may get benefit from using daily low dose Acetylsalicylic acid (aspirin 81 mg/d) to inhibit arachidonic acid conversion to prostaglandins G2 and H2, known precursors of thromboxane, and consequently decrease the risk for serious cardiovascular events[202].

SURGERY

Bariatric surgery is presently the most successful approach for sustained and significant weight loss and recovery of the associated comorbidities[203]. Bariatric surgery is beneficial in improving diabetes through the increase in β-cell function and/or mass, increasing insulin secretion, and decreasing IR [204]. Numerous researchers have investigated IR and β-cell function changes after different kinds of bariatric procedures. A meta-analysis by Rao *et al*[205] showed that gastric bypass, biliopancreatic diversion, and sleeve gastrectomy produce an early decrease in IR (within two weeks) through yet unknown mechanisms. Sleeve gastrectomy had an earlier reduction in IR than gastric banding. A Dutch study showed increased acceptance of bariatric surgery by the pediatricians, parents, and adolescents as a therapeutic in children and adolescents with severe obesity who do not respond to lifestyle intervention[206]. However, intestinal bypass surgery in children should possibly only be used in cases of potentially life-threatening complications of obesity such as IR, OSA, dyslipidemia, hypertension, non-alcoholic fatty liver diseases, and bone and joint problems[207].

TREATMENT OF SPECIFIC CASES WITH IR

The treatment can be individualized in certain pathological conditions.

CONGENITAL GENERALIZED LIPODYSTROPHY

Congenital generalized lipodystrophy (CGL) requires multidisciplinary management and should be adjusted according to the specific features of the patients and the severity of the dystrophy. It may involve psychological support, aesthetic surgery, and high carbohydrate and a low-fat diet. Exercise should be tailored according to the type, with regular exercise for type 1 CGL and avoidance of strenuous exercise for type 4. Patients with type 4 may require β-adrenergic blockers or other antiarrhythmic medications. Patients with type 2 CGL and cardiomyopathy should be assessed individually to ensure their fitness for exercise and avoid when needed[208]. The presence of severe hypertriglyceridemia in CGL could benefit from fibrate drugs. Low-dose statins could help to reduce non-HDL cholesterol. If the patients develop DM, Metformin and sulphonylureas are the first lines of therapy. Insulin is usually needed in very high doses[209]. Leptin levels are markedly decreased in patients with generalized lipodystrophy. Leptin analogs as metreleptin can improve metabolic profile in CGL type 1 and type 2. Metreleptin centrally reduces the appetite through its effects on the hypothalamus. Metreleptin has been Food and Drug Administration-approved since 2014 to treat congenital and acquired generalized lipodystrophy with significant improvement of the quality of life and physiological well-being[210].

LEPRECHAUNISM (DONOHUE SYNDROME)

Recombinant IGF-1 is the only treatment available to treat patients with leprechaunism so far through preventing compensatory hyperinsulinemia[211]. IGF-1 has a similar structure to insulin and can reduce blood glucose by 6% of the effect of insulin. It can attach to insulin receptors, enhance peripheral glucose uptake, induce glycogen synthesis, and decrease protein catabolism. The effectiveness of therapy with Recombinant IGF-1 is debatable, and we need further studies. However, evidence from the currently available small number of *in vivo* studies seems promising[212].

HYPERTENSION IN CHILDREN WITH IR AND OBESITY

The presence of hypertension in patients with MS and IR increases the risk of cardiovascular disease and premature death. Angiotensin-converting enzyme inhibitors positively affect hypertriglyceridemia and IR and are considered the first-line drugs in treating hypertension in children with obesity with additional renal and cardiovascular protective benefits[213,214]. However, we need more randomized, controlled, double-blind, and long-term studies for a definitive conclusion.

FATTY LIVER DISEASE

There is no specific pharmacologic treatment for fatty liver disease. The patients should start a low-fat diet and change their lifestyle to a more active style, and be encouraged to exercise. Triglyceride-lowering drugs and antioxidants can also be used. Insulin sensitizers, such as metformin, showed efficacy in animal and human studies[215].

CONCLUSION

As obesity increases in children, IR becomes more prevalent in children and adolescents than before. There is a broad range of genetic and acquired causes of IR. Early recognition of IR in the Pediatric age could prevent many possible short and long-term complications. Both prevention and management of IR resistance in children depend on changing the lifestyle, dietary intervention, and physical modification. Pharmacotherapy is indicated in selected cases. Surgery could help manage specific cases of IR and should be chosen meticulously.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Al-Biltagi M, Bediwy AS, and Saeed NK collected the data and wrote and revised the manuscript.

Conflict-of-interest statement: No conflict of interest.

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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