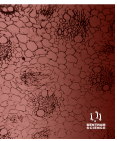


# Pathophysiology of Type 2 Diabetes in Children and Adolescents



Badhma Valaiyapathi<sup>1</sup>, Barbara Gower<sup>2</sup> and Ambika P. Ashraf<sup>3,\*</sup>

<sup>1</sup>Department of Epidemiology, School of Public Health, The University of Alabama at Birmingham, Birmingham, AL, USA; <sup>2</sup>Department of Nutrition Sciences, The University of Alabama at Birmingham, Birmingham, AL, USA; <sup>3</sup>Department of Pediatrics/Division of Pediatric Endocrinology and Metabolism, The University of Alabama at Birmingham, Birmingham, AL, USA

**Abstract: Background:** The prevalence of type 2 diabetes (DM) in children is disturbingly increasing in parallel with the increasing childhood obesity. Better knowledge regarding the pathophysiology of type 2 DM in children is paramount to devise an effective management plan.

**Objective:** Discuss the pathophysiology of type 2 DM in children and adolescents.

**Methods and Results:** This is a comprehensive review of the literature on this topic. Type 2 DM in childhood is viewed as a continuum of insulin resistance (IR) which is determined by an underlying genetic predisposition, intrauterine environment, excessive food consumption, continued rapid weight gain, and poor lifestyle. Besides IR, this is compounded by multiple metabolic defects including  $\beta$ -cell dysfunction and inadequate insulin secretion,  $\alpha$ -cell dysfunction, hyperglucagonemia and increased hepatic glucose production, lipotoxicity, inflammation, deficiencies in incretin production and action, and increased renal glucose reabsorption. The confluence of genetic and environmental factors underscores the complexity in disease progression.

**Conclusion:** A consistent single risk factor for type 2 DM is obesity and related IR and therefore it is essential to curtail the progression of obesity. It is important to investigate the role of stringent dietary and nutritional approaches, medications that enhance  $\beta$ -cell function and insulin sensitivity.

## ARTICLE HISTORY

Received: March 24, 2018  
Revised: May 24, 2018  
Accepted: June 03, 2018

DOI:  
10.2174/1573399814666180608074510



CrossMark

**Keywords:** Type 2 diabetes, obesity, insulin resistance, insulin secretion, hyperglycemia, hyperglucagonemia, incretin.

## 1. INTRODUCTION

Over the past 20 years, the prevalence of type 2 diabetes mellitus (DM) among children and adolescents has increased several folds in the United States [1-4] and the world [5, 6]. This increase among the pediatric age group is aligned with a parallel increase in childhood obesity. Notwithstanding that the prevalence of obesity is no longer increasing in the United States, the prevalence of type 2 DM has increased thrice in this age group, related to the increasing degree of severe childhood obesity among children and adolescents.

Compared to adults with type 2 DM who develop secondary complications at a later age despite being insulin resistant for years, children develop clinical DM and complications more rapidly and aggressively [7]. Adolescents with type 2 DM have very poor treatment outcomes and a rapid decline in their glycemic control with the current treatment protocols [8-12]. Patients with type 2 DM have a cluster of metabolic risk factors including obesity, Insulin Resistance

(IR), hyperglycemia, dyslipidemia, hypertension, ectopic fat deposition and inflammation which predispose them to future cardiovascular disease (CVD) [5]. Data from the SEARCH for Diabetes in Youth study (SEARCH study) and the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial revealed a higher prevalence of atherogenic dyslipidemia, hypertension and albuminuria among youth with type 2 DM [11, 13]. Early onset of type 2 DM and prolonged exposure to these metabolic abnormalities amplifies the long-term micro and macrovascular complications of these children. Microvascular complications are present even as early as the diagnosis which infers an earlier appearance of clinical complications as opposed to children with type 1 DM.

The purpose of this article is to provide in-depth pathophysiology of type 2 DM in children which may provide a roadmap of potential management strategies.

## 2. MATERIALS AND METHODS

We performed a computerized PubMed search of English language original and review articles. This review provides a comprehensive summary of the unique pathophysiology of type 2 DM in children and adolescents.

\*Address correspondence to this author at the Department Pediatric Endocrinology, The University of Alabama at Birmingham, Birmingham, AL 35233, USA; Tel: 205 638 9107, Fax: 205 638 9821; E-mail: [aashraf@peds.uab.edu](mailto:aashraf@peds.uab.edu)

### 3. RESULTS AND DISCUSSION

The core metabolic factors in the development of type 2 DM in children:

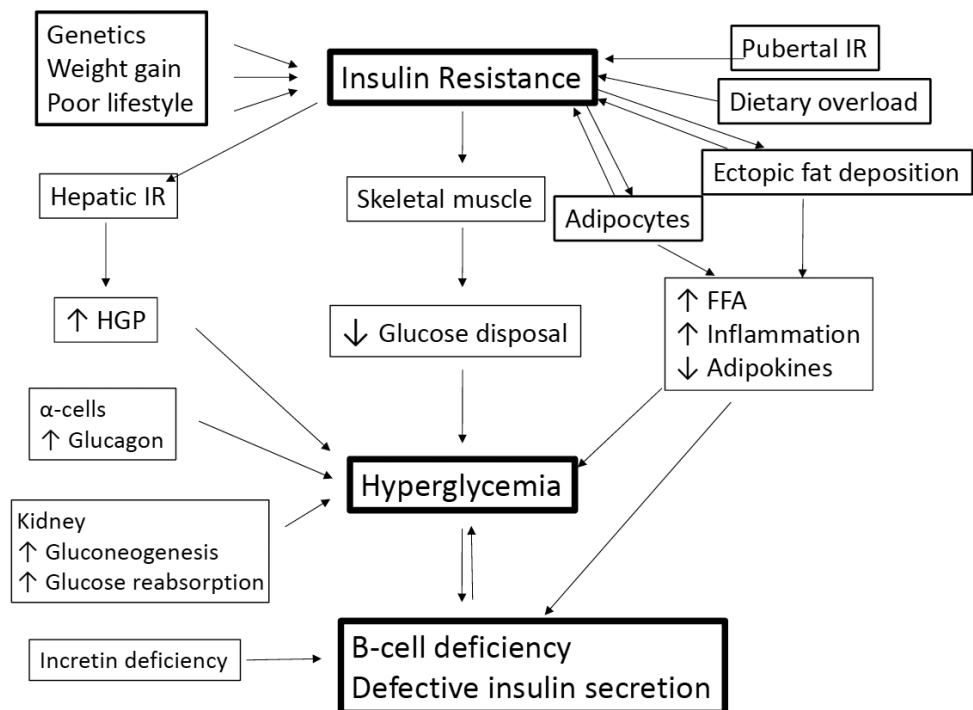
The core pathophysiologic defects include IR in the liver, muscle, adipose tissue, and eventual  $\beta$ -cell failure (Fig. 1). IR is the earliest metabolic abnormality that is present for years before the onset of type 2 DM. Overweight/obesity, continued weight gain, degree of weight gain, increasing Body Mass Index (BMI) percentiles, and consequent IR are the critical factors associated with the development of type 2 DM in children and adolescents [14-16]. Gaps exist on the best indicator of obesity, especially in ethnic minorities such as South Asians who have a higher predisposition for abdominal and visceral fat accumulation [17]. Therefore, some ethnicities may not require similar degrees of elevated BMI as other ethnicities to manifest type 2 DM [18]. Among the obese individuals, there is heterogeneity of fat composition with varying amounts of Visceral Adipose Tissue (VAT), Subcutaneous Adipose Tissue (SAT), and Brown Adipose Tissue (BAT) [19]. Even though BMI is traditionally considered as an indicator of obesity, excessive VAT predicts the development of cardiometabolic abnormalities such as IR, type 2 DM, chronic low-grade inflammation, atherogenic dyslipidemia, and hypertension [19, 20]. Ectopic fat accumulation includes storage of fat in non-adipose tissue such as myocardial and epicardial fat, intra and retroperitoneal fat, mesenteric fat, etc. On the other hand, brown adipose tissue has a positive influence in preventing type 2 DM. Both BMI and waist circumference are inadequate to assess the visceral adiposity.

Prevalence of type 2 DM is more common among children in the age group between 10 and 19 years, corresponding to the hormonal dynamics of puberty [6, 8,

21-23]. During puberty, there is a surge in growth hormone and Insulin-like Growth Factor-I (IGF-1), which increases IR [24]. Increased production of growth hormone and IGF-1 leads to IR through increased lipid breakdown and increased Free Fatty Acids (FFA) in the circulation. Almost always, the growth hormone driven IR is transient, and any hyperglycemia reverts to normal after puberty. Similarly, an increase in sex hormones during puberty, especially androstenedione, increases the Acute Insulin Response (AIR), which is an independent predictor of type 2 DM [25, 26]. Girls are more likely to develop type 2 DM than boys [3]. Insulin receptors on  $\beta$ -cells get overstimulated by pubertal estrogen, or environmental/exogenous estrogens, rendering  $\beta$ -cells more vulnerable at the time of higher  $\beta$ -cell turnover. This, in turn, is postulated to result in excessive insulin signaling, exacerbation of IR and ultimately to  $\beta$ -cell exhaustion [27]. Obese children who develop type 2 DM around puberty tend to deteriorate their diabetes control likely due to continued weight gain, increasing the degree of their obesity and persistent IR even post-puberty.

Puberty is not the single inciting factor insofar as many children are diagnosed before the onset of puberty [28, 29]. Maternal health during pregnancy, especially maternal diabetes, birth weight, post-natal rapid weight gain and type of body fat accrual after birth also contribute to the development of type 2 DM later in life [30-33].

The decline in insulin sensitivity heralds the progression from Normal Glucose Tolerance (NGT) to Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT) to type 2 DM [34, 35]. The progression from NGT through stages of IFG, IGT and type 2 DM is not always sequential [35-39]. A decreased first phase insulin secretion and glucose disposition index (product of insulin sensitivity and  $\beta$ -cell function) are the hallmark of IGT which can progress to



**Fig. (1).** Pathophysiology of type 2 diabetes in children and adolescents. HGP- Hepatic Glucose Production, IR- Insulin Resistance, FFA- Free Fatty Acid.

defective second phase insulin secretion [35]. Reduced glucose clearance after an intravenous glucose tolerance test (GTT) and high insulin response following an oral GTT are individual risk factors for type 2 DM [40]. Compensatory hypersecretion of insulin exacerbates oxidative stress, rapid decline in  $\beta$ -cell function and ultimately leads to attenuated insulin secretion [41-43]. The development of IGT indicates a significant functional defect of  $\beta$ -cell, *i.e.*, about 80% of  $\beta$ -cell insulin secretory function is lost [44]. Persistent hyperglycemia further exacerbates  $\beta$ -cell damage (glucotoxicity) [45].

A strong genetic predisposition is a crucial determinant for developing T2DM [46-49]. Parental diabetes is a risk factor for the development of type 2 DM [14]. Factors that trigger the phenotypic expression of the T2DM are the rapidity and degree of weight gain, consumption of high calorie- high fat- high carbohydrate-high protein food, physical inactivity, and certain diabetes- inducing medications which are additive to the genetic susceptibility (gene-environment interaction). Genome-Wide Association Sequence (GWAS) studies have identified more than 65 genetic variants that increase the risk of developing type 2 DM. Most of these several Single Nucleotide Polymorphisms (SNPs) have an independent risk (INCOMPLETE) that is

significantly small effect in causing T2DM. These could be modulated in the presence of environmental, non-genetic secondary factors that increase their susceptibility to the phenotypic expression of T2DM. Of these the genetic loci, some of the genes involved in either the production of glucose,  $\beta$ - cell function, insulin sensitivity, insulin signaling, pancreas development, and monogenic diabetes are *TCF7L2*, *PPARG*, *HNFA1*, *HNF1B*, *HNF4A*, *MC4R*, *GIPR*, *GCKR*, *FTO*, *KCNJ11*, *KCNQ1*, *KCNQ1*, *GLIS3*, *NOTCH2*, *WFS1*, *IGFBP2*, *SLC30A8*, *HHEX*, *CDKN2A*, *CF7L2*, *CDKAL1*, *JAZF1* [50-59]. Table 1 illustrates common SNPs variants associated with future risk of T2DM. Table summarizes the genetic variants that are significantly associated with the risk of type 2 DM independent of clinical risk factors with their odds ratios.

Even though traditionally type 2 DM is characterized by the lack of  $\beta$ -cell autoantibodies, antibody positivity is observed in some cases. This variant of type 2 DM is called type 1.5 DM or double DM or latent autoimmune diabetes in youth [60, 61]. Overlap of autoimmunity is thought to accelerate the progression towards  $\beta$ -cell deficiency and insulin dependency. Rapid metabolic decline and accelerated progressions towards insulin tendency are frequently observed in children with type 2 DM [11, 12]. The rapidity of  $\beta$ -cell

**Table 1. Common genetic locus associated with risk of type 2 diabetes.**

Genetic Locus	SNP	Chromosome	Risk Allele	Published Odds Ratio	Published P Value
NOTCH2	rs10923931	1	T	1.13	$6.7 \times 10^{-6}$
BCL11A	rs10490072	2	T	1.05	$4.9 \times 10^{-5}$
THADA	rs7578597	2	T	1.15	$1.1 \times 10^{-4}$
IGF2BP2	rs1470579	3	C	1.14	$8.9 \times 10^{-16}$
PPARg	rs1801282	3	C	1.14	$1.7 \times 10^{-6}$
ADAMTS9	rs4607103	3	C	1.09	$3.1 \times 10^{-4}$
WFS1	rs10010131	4	G	1.12	0.02
CDKAL1	rs7754840	6	C	1.12	$4.1 \times 10^{-11}$
VEGFA	rs9472138	6	T	1.06	$4.1 \times 10^{-5}$
JAZF1	rs864745	7	T	1.10	$4.6 \times 10^{-5}$
SLC30A8	rs13266634	8	C	1.12	$5.3 \times 10^{-8}$
CDKNA/2B	rs10811661	9	T	1.20	$7.8 \times 10^{-15}$
HHEX	rs1111875	10	C	1.13	$5.7 \times 10^{-10}$
CDC123	rs12779790	10	G	1.11	$4.7 \times 10^{-5}$
TCF7L2	rs7903146	10	T	1.37	$1.0 \times 10^{-48}$
KCNJ11	rs5219	11	T	1.14	$6.7 \times 10^{-11}$
INS	rs689	11	T	1.93	$2.0 \times 10^{-2}$
DCD	rs1153188	12	A	1.08	$3.2 \times 10^{-5}$
TSPAN8	rs7961581	12	C	1.09	$3.7 \times 10^{-5}$
FTO	rs8050136	16	C	1.17	N/A

Legend: Table summarizes the gent variants that are significantly associated with the risk of type 2 DM independent of clinical risk factors with their odds ratios.

decline is accelerated in children compared to adults likely due to the vulnerability of the  $\beta$ -cell during a period of dynamic growth and maturation, the synergy between pubertal IR with IR of obesity, severity, and rapidity of weight gain, and the interplay of growth hormone, insulin, estrogen and other sex steroids.

#### 4. INSULIN RESISTANCE

Type 2 DM is a continuum of IR. Even though the risk for IR may be mostly genetically determined, heritability is still not completely understood [62-64]. Moreover, IR is more pronounced by obesity and a sedentary lifestyle. Unlike their adult counterparts, children tend to overproduce insulin disproportionately in response to IR. While hepatic IR and impaired first phase insulin secretion are attributed to the development of IFG, peripheral IR is attributed to the worsening of glucose disposition and IGT. Studies have shown that peripheral IR plays a significant role in the initiation of type 2 DM [65].

Muscle IR contributes to 85-90% of reduced total body glucose disposal in individuals with type 2 DM. Impaired uptake of glucose in the peripheral tissues (liver, adipose tissue, and especially skeletal muscle) and increased HGP, as a result of the loss of negative feedback mechanism from glucose, promote hyperglycemia. The excess accumulation of fat in the liver, muscle and  $\beta$ -cells increase IR in these organs [44]. Increased intramyocellular lipid content is seen in children with obesity and exacerbates IR [66]. Increased FFA in the circulation (lipotoxicity) disrupts insulin signaling pathways and contributes to skeletal muscle insulin resistance. Abnormal insulin signaling underlines the defect in glucose transport [44]. Augmented FFA production in IR/insulin deficient states can exacerbate HGP [67]. Pro-inflammatory chemokines and cytokines, produced in chronic low-grade obesity-induced inflammation, cause worsening of IR (vide infra).

Mitochondrial dysfunction is also a known factor in the development of IR. The inability of mitochondria in the liver and skeletal muscle to effectively oxidize fatty acids contribute to IR. This, in turn, affects the normal insulin signaling pathway in the peripheral tissues [68].

#### 5. INSULIN SECRETORY DEFICIENCY

Defects in insulin secretion along with IR beget IGT and type 2 DM given the inability of the  $\beta$ -cell to respond to incremental changes in glucose. Insulin secretory defects contribute to the development of elevated fasting glucose and IGT. Similar to IR, insulin secretory defects can occur during the early stages of the disease ultimately resulting in rapid progression of IGT to type 2 DM in children. Impaired insulin secretion is a result of defective production in  $\beta$ -cells as well as decreased  $\beta$ -cell mass, the latter more pronounced among obese children compared to their normal weight counterpart [68, 69]. Studies have shown that insulin secretion in relation to insulin sensitivity is found to decline with the disease progression from IGT to type 2 DM. In addition to IR, adults have an impaired insulin release, even at the early stages of developing IGT [44, 70]. However, among obese children who have IGT, there is no significant impairment in the second phase of insulin secretion in

response to IR. However, obese children who have overt type 2 DM manifest impaired  $\beta$ -cell function with combined reduced first phase and second phase insulin release following an oral glucose load [34, 39].

Role of proinsulin: IR in peripheral tissues results in increased production of proinsulin from the pancreatic  $\beta$ -cells. This is accompanied by a defect in the terminal cleavage of proinsulin to insulin leading to hyperproinsulinemia [71]. In children, proinsulin to insulin ratio is found to be increased only during the overt disease, unlike adults where the ratio is increased even as early as at the IGT stage [70, 72]. This could be partly explained by the fact that the production and cellular metabolism of proinsulin are age-dependent [68]. Compared to children with hyperglycemia, adults tend to lose the processing ability at a faster pace [34, 68]. Therefore, proinsulin may not be a reliable marker of  $\beta$ -cell function in IGT stages in children.

#### 6. INCREASED HEPATIC GLUCOSE PRODUCTION

Hepatic IR: Following a meal, the secretion of insulin stimulates liver glucose uptake and glycogen storage which then suppress HGP. Due to hepatic IR, there is a failure to inhibit glycogenolysis and inability to suppress gluconeogenesis. Continued HGP along with reduced glucose uptake in peripheral tissue, such as skeletal muscle, results in persistent hyperglycemia [73]. The antithetical tandem of glucagon and insulin control HGP, by modulating enzyme flux and gene transcription [74]. The increased IR in the brain can augment HGP via neural signaling, independent of hepatic IR.

Hyperglucagonemia: In patients with type 2 DM, as a result of reduced insulin secretion and  $\alpha$ -cell insulin resistance, the production of glucagon is not as tightly inhibited, leading to increased HGP [75, 76]. Moreover, there is also enhanced hepatic sensitivity to glucagon. Patients have increased glucagon concentration in the fasting state which is found to increase paradoxically following a carbohydrate meal. This is especially disconcerting given the fact that it occurs in a setting of hyperglycemia and hyperinsulinemia which would typically suppress plasma glucagon levels. Chronic  $\beta$ -cell dysfunction might result in  $\alpha$ -cell dysfunction which would be a plausible explanation for this paradoxical glucagon increase postprandially. Increased glucagon secretion by the pancreatic  $\alpha$ -cells plays an essential role along with 'relative' hypoinsulinemia in the pathogenesis of type 2 DM, *i.e.*, the 'bi-hormonal hypothesis' of type 2 DM [76, 77]. In children with type 2 DM, hyperglucagonemia is determined by the duration of diabetes [78]. An increase in the  $\alpha$ -cell mass in response to decreasing  $\beta$ -cell mass may also contribute to hyperglucagonemia typical of type 2 DM patients. Hyperglucagonemia plays a vital role in the progression from normoglycemia to IGT and may foretell IGT [77].

#### 7. DYSREGULATION OF FAT METABOLISM

There are multiple dysregulated metabolic pathways ranging from increased FFA flux from adipose tissue, increased hepatic *De Novo* Lipogenesis (DNL) from excessive carbohydrate consumption, and elevated plasma

Triglycerides (TG) that accelerate the progression from normal glucose tolerance to impaired GTT and diabetes.

**Elevated FFA:** Insulin plays a critical role in adipocyte lipogenesis by stimulating glucose transport and inhibiting lipolysis by Hormone-Sensitive Lipase (HSL). In the postprandial state, insulin ensures TG clearance and FFA delivery to adipocytes by enhancing actions of Lipoprotein Lipase (LPL). In obese individuals, there is adipocyte resistance to the anti-lipolytic actions of insulin and functional impairment in lipid storage in adipocytes which lead to increased FFA flux, systemic inflammation, and increased lipid accumulation in non-adipose tissues, such as skeletal muscle, liver, and  $\beta$ -cells. This fat accretion in non-adipose tissues promotes IR by affecting normal glucose metabolism [78, 79]. Elevated FFAs impede insulin's ability to suppress HGP, stimulate gluconeogenesis, decrease glucose uptake in peripheral tissues, worsen hepatic IR and negatively impact insulin secretion [67, 80-84]. Chronically elevated levels of FFAs cause lipotoxicity, increased HGP, and pancreatic  $\beta$ -cell death [85]. In sum, disturbed fatty acid metabolism in adipose tissue, liver, gut, pancreas, and skeletal muscle acting in concert lead to the increased peripheral IR and insulin deficiency.

**Circulating plasma TG and dyslipidemia:** Elevated plasma TG is common in IR states, and there is likely a bi-directional relationship between IR and elevated plasma TG. Dyslipidemia is a known risk factor for type 2 DM in children [86]. Increased fasting TG has been associated with IGT in children [38]. Elevated plasma TG interferes with insulin signaling pathways and increases IR and reduction of TG results in lowering of IR [87]. There is enhanced very Low-Density Lipoprotein (VLDL) synthesis which leads to elevated TG and low LDL, and reduced HDL [80, 88].

**Lipogenesis in liver:** Chronic hyperinsulinemia and excessive carbohydrate consumption stimulate DNL by increased FA synthesis from excessive production of acetyl-CoA subunits generated from glycolysis of refined carbohydrates, glucose and fructose [89] and can lead to fat accumulation in the liver and Non-Alcoholic Fatty Liver Disease (NAFLD). Increased FFA flux from IR can also exceed hepatic capacity for FA oxidation leading to hepatic steatosis [90]. High-fat diets can also trigger increased FA oxidation and generation of acetyl-CoA [91]. NAFLD, in turn, dysregulates gluconeogenesis [92, 93].

**Adipocytokines and pro-inflammatory cytokines:** Expansion of adipose tissue leads to the overproduction of adipocytokines exacerbating the metabolic dysfunction. Excess or deficiency of adipocytokines such as leptin or adiponectin can unfavorably impact insulin sensitivity [81, 94]. Various pro-inflammatory cytokines augment IR in an obese individual, especially pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF)- $\alpha$ , Interleukin (IL) -1, IL-1 $\beta$ , IL-6, IL-8 and Interferon- $\alpha$  (IFN- $\alpha$ ) among several others [95, 96]. Chronic exposure to these inflammatory cytokines leads to the activation of cytokine signaling proteins, inactivation of insulin signaling receptors in the pancreatic  $\beta$ -cells, all of which promote lipolysis, hepatic IR and dyslipidemia. Similarly, intracellular lipid accumulation in liver and skeletal muscle exacerbates IR through proinflammatory cytokines [97]. Besides leading to IR, these

pro-inflammatory cytokines along with pancreatic-derived factor (PANDER) also result in pancreatic  $\beta$ -cell apoptosis [98].

## 8. ROLE OF DIET

Dietary management is an integral part of diabetes management. High caloric, high fat and high carbohydrate diet have been implicated in the development of T2DM. The standard American Diet, characterized by a high proportion of processed starches, high glycemic load, and added sugars, exacerbate these stresses on the physiological processes that regulate glucose metabolism.

Currently, there are no evidence-based guidelines or recommendations for macronutrient composition for children with type 2 DM. Remission of type 2 DM in adults was successfully reported with a very low-calorie diet [99]. However, there is limited data from Randomized Clinical Trials (RCTs) to support the effectiveness of these recommendations to induce meaningful reductions in the incidence of childhood type 2 DM. Weight loss through caloric restriction is unlikely to be practical in a growing population of children. Glucotoxicity and lipotoxicity which ensue during pre-diabetic IR state and following a dietary overload of glucose and FFA are factors which generate Reactive Oxygen Species (ROS) and oxidative stress with resultant generation of inflammatory mediators. The excess carbohydrate consumption is well known to enhance insulin release, trigger and worsen IR with the resultant increase in dyslipidemia and hyperglycemia. Short-term studies in adults suggest that, without restricting calories, change in diet composition alone by reducing intake of carbohydrate sources such as added sugars, high glycemic grains, and fructose can achieve weight loss and improved insulin sensitivity [100-102]. In adults with type 2 DM, a low carbohydrate diet resulted in a better lowering of HbA1C compared to low-fat diet, despite similar weight loss [103]. Theoretically low carbohydrate diet results in lower glycemic index foods, lesser carbohydrate consumption and improved insulin sensitivity [104]. High protein diet and increased circulating levels of branched-chain amino acids (BCAA), such as isoleucine, leucine, and valine could also serve as risk factors for developing type 2 DM [105]. Elevated circulating BCAA is thought to predict IR in obese children [106] and predict deterioration of glycemic control in adolescents [107]. The implication of macronutrient composition of the diet is not completely clear [108] and warrants further investigation with the comparison between low carbohydrate and low-fat dietary modalities long term.

**Increased renal glucose reabsorption:** Renal tubular threshold for glucose reabsorption is raised in individuals with type 2 DM resulting in increased renal reabsorption of glucose [109].

**Incretin deficiency or resistance:** Incretins are enteroendocrine gut hormones produced following food ingestion and account for nearly 70% of insulin secretion after a meal. Type 2 DM is known to have impaired or absent incretin insulinotropic effect. Studies have shown that apart from the impaired insulinotropic effect, reduced incretin secretion may also contribute to type 2 DM [94, 110]. Glucagon-like Peptide-1 (GLP-1) and Glucose-

dependent Insulinotropic Peptide (GIP) are the two key incretins that account for >90% of the incretin effect [44]. GLP-1 promotes  $\beta$ -cell proliferation and survival, suppresses glucagon secretion and alters gastric emptying, all of which contribute to glucose lowering. Also, GLP-1 enhances insulin sensitivity and peripheral glucose utilization. GLP-1 receptor agonist may emerge as a mainstay of treatment for adult type 2 DM. Youth with type 2 DM manifest a reduced incretin effect compared with their normal glucose tolerant counterparts, without significant differences in GLP-1 and GIP concentrations [111].

## 9. FACTORS INHERENT TO THE PANCREAS

Size of the pancreas: In children without DM, the parenchymal and fat volume of the pancreas increase linearly up until the age of 20. Increase in BMI has a positive association with pancreas volume [112]. Obese individuals have a larger pancreas size compared to overweight individuals, and the latter exceeds those of normal weight [113]. Since obesity and IR are interrelated and concomitant, an increased pancreas size among individuals with IGT and insulin resistance can be postulated. However, with prolonged hyperglycemia in long-standing type 2 DM and with the progressive decline in insulin secretion, pancreas volume may actually decrease. Currently, there are no studies which analyze the volume of the pancreas in children and adolescents with type 2 DM. Autopsy studies have shown significant loss of  $\beta$ -cell volume from NGT to overt type 2 DM in adults, and this finding suggests that 50% of the  $\beta$ -cell volume is diminished by the 'pre-diabetes' stage [114]. Magnetic Resonance Imaging (MRI) in adults with type 2 DM showed a 33% decrease in pancreatic volume among those with recently diagnosed type 2 DM compared to normal individuals. Ectopic fat deposition and increased pancreatic fat content are associated with type 2 DM and a reduction in pancreatic TG deposition with weight loss correlates with improved insulin secretion. This infers that increased pancreatic fat deposition among obese individuals attenuates insulin secretory ability that reverts with weight reduction [115]. Furthermore, amylin is deposited in the pancreatic islet cells in individuals with long-standing hyperglycemia and is thought to affect the  $\beta$ -cell function adversely.

## CONCLUSION

The pathophysiology of type 2 DM in children and adolescents has some unique components. The progression of the disease occurs at a more rapid pace leading to the development of comorbidities at an early age which reinforces the need for early detection at the pre-diabetes stage. There are several deficiencies in the current management approach. A major hurdle is how to prevent or treat IR early insofar as the progression from IR to type 2 DM is a continuum. Intuitively, because the initial inciting factor is IR, an intense lifestyle program to ameliorate continued weight gain is mandatory to halt the progression of type 2 DM. Even though there is ample evidence that weight gain and increasing BMI percentiles are the culprits in the epidemic of type 2 diabetes in children, aggressive management of obesity is not incorporated as part of the treatment. We

need to amend strategies for patient education since the current patient education techniques have not inevitably translated to behavioral changes. It is essential to alter the trajectory of the weight gain to prevent the development of diabetes.

Even though adult data are showing that restricting calories can result in the remission of type 2 DM [99], dietary modifications focusing on calorie restriction are harder to initiate and sustain in children. It is essential to have an acceptable and sustainable dietary intervention where calories are not restricted. Prospective RCTs concerning the macronutrient composition of diet for obese children are indicated. Earlier diagnosis and management of diabetes increased the chance of durable glycemic control, and hence early identification of cases of type 2 DM is important [116].

A paradigm shift focusing on how to effectively treat the functional  $\beta$ -cell defects,  $\beta$ -cell loss, and other metabolic defects, while allowing for weight loss is paramount. Even though traditional insulin treatment for uncontrolled type 2 DM corrects the glucotoxicity and lipotoxicity, the core metabolic defect, namely, IR, is not ameliorated by insulin treatment. Moreover, insulin treatment is expensive, not well tolerated, leads to weight gain, and involves significant involvement from families and providers which result in barriers to medication adherence. The currently approved metformin is a mild insulin sensitizer with reports of poor treatment adherence and poor glycemic control outcomes [8, 9, 11, 12]. There are no comparative studies on insulin treatment vs. other agents in literature in children with type 2 DM. Well-designed prospective pediatric RCTs are needed to replicate their encouraging results in adults.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

- [1] Arslanian S. Type 2 diabetes in children: clinical aspects and risk factors. *Horm Res* 2002; 57(Suppl. 1): 19-28. PMID: 11979018
- [2] Rodriguez BL, Fujimoto WY, Mayer-Davis EJ, *et al.* Prevalence of cardiovascular disease risk factors in U.S. children and adolescents with diabetes: the SEARCH for diabetes in youth study. *Diabetes Care* 2006; 29(8): 1891-6. <http://dx.doi.org/10.2337/dc06-0310> PMID: 16873798
- [3] Mayer-Davis EJ, Lawrence JM, Dabelea D, *et al.* Search for diabetes in youth study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med* 2017; 376(15): 1419-29. <http://dx.doi.org/10.1056/NEJMoa1610187> PMID: 28402773
- [4] Dabelea D, Mayer-Davis EJ, Saydah S, *et al.* SEARCH for diabetes in youth study. Prevalence of type 1 and type 2 diabetes among

- children and adolescents from 2001 to 2009. *JAMA* 2014; 311(17): 1778-86.  
<http://dx.doi.org/10.1001/jama.2014.3201> PMID: 24794371
- [5] Reinehr T. Type 2 diabetes mellitus in children and adolescents. *World J Diabetes* 2013; 4(6): 270-81.  
<http://dx.doi.org/10.4239/wjd.v4.i6.270> PMID: 24379917
- [6] Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 2005; 146(5): 693-700.  
<http://dx.doi.org/10.1016/j.jpeds.2004.12.042> PMID: 15870677
- [7] Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. *Lancet* 2007; 369(9575): 1823-31.  
[http://dx.doi.org/10.1016/S0140-6736\(07\)60821-6](http://dx.doi.org/10.1016/S0140-6736(07)60821-6) PMID: 17531891
- [8] Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. International Society for Pediatric and Adolescent Diabetes. ISPAD clinical practice consensus guidelines 2006-2007. Type 2 diabetes mellitus in the child and adolescent. *Pediatr Diabetes* 2008; 9(5): 512-26.  
<http://dx.doi.org/10.1111/j.1399-5448.2008.00429.x> PMID: 18694453
- [9] Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2002; 25(1): 89-94.  
<http://dx.doi.org/10.2337/diacare.25.1.89> PMID: 11772907
- [10] Bacha F, Gungor N, Lee S, Arslanian SA. Progressive deterioration of  $\beta$ -cell function in obese youth with type 2 diabetes. *Pediatr Diabetes* 2013; 14(2): 106-11.  
<http://dx.doi.org/10.1111/j.1399-5448.2012.00915.x> PMID: 22913617
- [11] Zeitler P, Hirst K, Pyle L, et al. TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012; 366(24): 2247-56.  
<http://dx.doi.org/10.1056/NEJMoa1109333> PMID: 22540912
- [12] Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. *Am Fam Physician* 2009; 79(1): 29-36. PMID: 19145963
- [13] Albers JJ, Marcovina SM, Imperatore G, et al. Prevalence and determinants of elevated apolipoprotein B and dense low-density lipoprotein in youths with type 1 and type 2 diabetes. *J Clin Endocrinol Metab* 2008; 93(3): 735-42.  
<http://dx.doi.org/10.1210/jc.2007-2176> PMID: 18089692
- [14] Tanamas SK, Reddy SP, Chambers MA, Clark EJ, Dunnigan DL, Hanson RL, et al. Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population. *Pediatr Diabetes* 2017. PMID: 29282818
- [15] Abbasi A, Juszczyk D, van Jaarsveld CHM, Gulliford MC. Body Mass Index and Incident Type 1 and Type 2 Diabetes in Children and Young Adults: A Retrospective Cohort Study. *J Endocr Soc* 2017; 1(5): 524-37.  
<http://dx.doi.org/10.1210/js.2017-00044> PMID: 29264507
- [16] D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. *Diabetes Care* 2011; 34(Suppl. 2): S161-5.  
<http://dx.doi.org/10.2337/dc11-s212> PMID: 21525449
- [17] Shaw ND, Seminara SB, Welt CK, et al. Expanding the phenotype and genotype of female GnRH deficiency. *J Clin Endocrinol Metab* 2011; 96(3): E566-76.  
<http://dx.doi.org/10.1210/jc.2010-2292> PMID: 21209029
- [18] Haines L, Wan KC, Lynn R, Barrett TG, Shield JP. Rising incidence of type 2 diabetes in children in the U.K. *Diabetes Care* 2007; 30(5): 1097-101.  
<http://dx.doi.org/10.2337/dc06-1813> PMID: 17259470
- [19] González N, Moreno-Villegas Z, González-Bris A, Egado J, Lorenzo Ó. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. *Cardiovasc Diabetol* 2017; 16(1): 44.  
<http://dx.doi.org/10.1186/s12933-017-0528-4> PMID: 28376896
- [20] Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care* 2000; 23(4): 465-71.  
<http://dx.doi.org/10.2337/diacare.23.4.465> PMID: 10857936
- [21] Copeland KC, Zeitler P, Geffner M, et al. TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab* 2011; 96(1): 159-67.  
<http://dx.doi.org/10.1210/jc.2010-1642> PMID: 20962021
- [22] Pinhas-Hamiel O, Lerner-Geva L, Copperman NM, Jacobson MS. Lipid and insulin levels in obese children: changes with age and puberty. *Obesity (Silver Spring)* 2007; 15(11): 2825-31.  
<http://dx.doi.org/10.1038/oby.2007.335> PMID: 18070774
- [23] Arslanian SA. Type 2 diabetes mellitus in children: pathophysiology and risk factors. *J Pediatr Endocrinol Metab* 2000; 13(Suppl. 6): 1385-94.  
<http://dx.doi.org/10.1515/jpem-2000-s612> PMID: 11202214
- [24] Flint A, Arslanian S. Treatment of type 2 diabetes in youth. *Diabetes Care* 2011; 34(Suppl. 2): S177-83.  
<http://dx.doi.org/10.2337/dc11-s215> PMID: 21525452
- [25] Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. *Diabetes* 2001; 50(11): 2444-50.  
<http://dx.doi.org/10.2337/diabetes.50.11.2444> PMID: 11679420
- [26] Kelsey MM, Zeitler PS. Insulin Resistance of Puberty. *Curr Diab Rep* 2016; 16(7): 64.  
<http://dx.doi.org/10.1007/s11892-016-0751-5> PMID: 27179965
- [27] Nadal A, Alonso-Magdalena P, Soriano S, Quesada I, Ropero AB. The pancreatic beta-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. *Mol Cell Endocrinol* 2009; 304(1-2): 63-8.  
<http://dx.doi.org/10.1016/j.mce.2009.02.016> PMID: 19433249
- [28] Beck J, Brandt EN Jr, Blackett P, Copeland K. Prevention and early detection of type 2 diabetes in children and adolescents. *J Okla State Med Assoc* 2001; 94(8): 355-61. PMID: 11515385
- [29] Taha DR, Castells S, Umpaichitra V, Bastian W, Banerji MA. Beta-cell response to intravenous glucagon in African-American and Hispanic children with type 2 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002; 15(1): 59-67.  
<http://dx.doi.org/10.1515/JPEM.2002.15.1.59> PMID: 11822582
- [30] Jiang X, Ma H, Wang Y, Liu Y. Early life factors and type 2 diabetes mellitus. *J Diabetes Res* 2013; 2013:485082  
<http://dx.doi.org/10.1155/2013/485082> PMID: 24455747
- [31] Menke A, Casagrande S, Cowie CC. Prevalence of Diabetes in Adolescents Aged 12 to 19 Years in the United States, 2005-2014. *JAMA* 2016; 316(3): 344-5.  
<http://dx.doi.org/10.1001/jama.2016.8544> PMID: 27434447
- [32] Dabelea D, Mayer-Davis EJ, Lamichhane AP, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. *Diabetes Care* 2008; 31(7): 1422-6.  
<http://dx.doi.org/10.2337/dc07-2417> PMID: 18375420
- [33] Pettitt DJ, Talton J, Dabelea D, et al. SEARCH for Diabetes in Youth Study Group. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. *Diabetes Care* 2014; 37(2): 402-8.  
<http://dx.doi.org/10.2337/dc13-1838> PMID: 24041677
- [34] Bacha F, Lee S, Gungor N, Arslanian SA. From pre-diabetes to type 2 diabetes in obese youth: pathophysiological characteristics along the spectrum of glucose dysregulation. *Diabetes Care* 2010; 33(10): 2225-31.  
<http://dx.doi.org/10.2337/dc10-0004> PMID: 20592052
- [35] Bacha F, Gungor N, Lee S, Arslanian SA. In vivo insulin sensitivity and secretion in obese youth: what are the differences between normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes? *Diabetes Care* 2009; 32(1): 100-5.  
<http://dx.doi.org/10.2337/dc08-1030> PMID: 18835946
- [36] Cali' AM, Bonadonna RC, Trombetta M, Weiss R, Caprio S. Metabolic abnormalities underlying the different prediabetic phenotypes in obese adolescents. *J Clin Endocrinol Metab* 2008; 93(5): 1767-73.  
<http://dx.doi.org/10.1210/jc.2007-1722> PMID: 18303080
- [37] Cali AM, Man CD, Cobelli C, et al. Primary defects in beta-cell function further exacerbated by worsening of insulin resistance mark the development of impaired glucose tolerance in obese adolescents. *Diabetes Care* 2009; 32(3): 456-61.  
<http://dx.doi.org/10.2337/dc08-1274> PMID: 19106382
- [38] Love-Osborne K, Butler N, Gao D, Zeitler P. Elevated fasting triglycerides predict impaired glucose tolerance in adolescents at risk for type 2 diabetes. *Pediatr Diabetes* 2006; 7(4): 205-10.  
<http://dx.doi.org/10.1111/j.1399-5448.2006.00179.x> PMID: 16911007

- [39] Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. Beta-cell function across the spectrum of glucose tolerance in obese youth. *Diabetes* 2005; 54(6): 1735-43. <http://dx.doi.org/10.2337/diabetes.54.6.1735> PMID: 15919795
- [40] Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states. Sequence of events leading to non-insulin-dependent diabetes mellitus. *J Clin Invest* 1994; 94(5): 1714-21. <http://dx.doi.org/10.1172/JCI117518> PMID: 7962519
- [41] Del Prato S, Penno G, Miccoli R. Changing the treatment paradigm for type 2 diabetes. *Diabetes Care* 2009; 32(Suppl. 2): S217-22. <http://dx.doi.org/10.2337/dc09-S314> PMID: 19875555
- [42] Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104(6): 787-94. <http://dx.doi.org/10.1172/JCI7231> PMID: 10491414
- [43] Weiss R, Santoro N, Giannini C, Galderisi A, Umamo GR, Caprio S. Prediabetes in youth - mechanisms and biomarkers. *Lancet Child Adolesc Health* 2017; 1(3): 240-8. [http://dx.doi.org/10.1016/S2352-4642\(17\)30044-5](http://dx.doi.org/10.1016/S2352-4642(17)30044-5) PMID: 29075659
- [44] DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; 58(4): 773-95. <http://dx.doi.org/10.2337/db09-9028> PMID: 19336687
- [45] Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care* 1990; 13(6): 610-30. <http://dx.doi.org/10.2337/diacare.13.6.610> PMID: 2192847
- [46] Florez JC. Pharmacogenetics in type 2 diabetes: precision medicine or discovery tool? *Diabetologia* 2017; 60(5): 800-7. <http://dx.doi.org/10.1007/s00125-017-4227-1> PMID: 28283684
- [47] Uwaifo GI, Fallon EM, Chin J, Elberg J, Parikh SJ, Yanovski JA. Indices of insulin action, disposal, and secretion derived from fasting samples and clamps in normal glucose-tolerant black and white children. *Diabetes Care* 2002; 25(11): 2081-7. <http://dx.doi.org/10.2337/diacare.25.11.2081> PMID: 12401760
- [48] Liese AD, D'Agostino RB Jr, Hamman RF, *et al.* SEARCH for Diabetes in Youth Study Group. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics* 2006; 118(4): 1510-8. <http://dx.doi.org/10.1542/peds.2006-0690> PMID: 17015542
- [49] Gower BA. Syndrome X in children: Influence of ethnicity and visceral fat. *Am J Hum Biol* 1999; 11(2): 249-57. [http://dx.doi.org/10.1002/\(SICI\)1520-6300\(1999\)11:2<249::AID-AJHB12>3.0.CO;2-#](http://dx.doi.org/10.1002/(SICI)1520-6300(1999)11:2<249::AID-AJHB12>3.0.CO;2-#) PMID: 11533948
- [50] Franks PW, Pearson E, Florez JC. Gene-environment and gene-treatment interactions in type 2 diabetes: progress, pitfalls, and prospects. *Diabetes Care* 2013; 36(5): 1413-21. <http://dx.doi.org/10.2337/dc12-2211> PMID: 23613601
- [51] Lyssenko V, Jonsson A, Almgren P, *et al.* Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* 2008; 359(21): 2220-32. <http://dx.doi.org/10.1056/NEJMoa0801869> PMID: 19020324
- [52] Meigs JB, Shrader P, Sullivan LM, *et al.* Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008; 359(21): 2208-19. <http://dx.doi.org/10.1056/NEJMoa0804742> PMID: 19020323
- [53] Lin X, Song K, Lim N, *et al.* Risk prediction of prevalent diabetes in a Swiss population using a weighted genetic score--the CoLauS Study. *Diabetologia* 2009; 52(4): 600-8. <http://dx.doi.org/10.1007/s00125-008-1254-y> PMID: 19139842
- [54] Saxena R, Voight BF, Lyssenko V, *et al.* Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007; 316(5829): 1331-6. <http://dx.doi.org/10.1126/science.1142358> PMID: 17463246
- [55] Zeggini E, Weedon MN, Lindgren CM, *et al.* Wellcome Trust Case Control Consortium (WTCCC). Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 2007; 316(5829): 1336-41. <http://dx.doi.org/10.1126/science.1142364> PMID: 17463249
- [56] Zeggini E, Scott LJ, Saxena R, *et al.* Wellcome Trust Case Control Consortium. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* 2008; 40(5): 638-45. <http://dx.doi.org/10.1038/ng.120> PMID: 18372903
- [57] Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes* 2000; 49(12): 2201-7. <http://dx.doi.org/10.2337/diabetes.49.12.2201> PMID: 11118026
- [58] Meigs JB, Dupuis J, Herbert AG, Liu C, Wilson PW, Cupples LA. The insulin gene variable number tandem repeat and risk of type 2 diabetes in a population-based sample of families and unrelated men and women. *J Clin Endocrinol Metab* 2005; 90(2): 1137-43. <http://dx.doi.org/10.1210/jc.2004-1212> PMID: 15562019
- [59] Frayling TM. Genome-wide association studies provide new insights into type 2 diabetes aetiology. *Nat Rev Genet* 2007; 8(9): 657-62. <http://dx.doi.org/10.1038/nrg2178> PMID: 17703236
- [60] Reinehr T, Schober E, Wiegand S, Thon A, Holl R. DPV-Wiss Study Group. Beta-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification? *Arch Dis Child* 2006; 91(6): 473-7. <http://dx.doi.org/10.1136/adc.2005.088229> PMID: 16449253
- [61] Awa WL, Boehm BO, Rosinger S, *et al.* DPV Initiative and the German BMBF Competence Networks Diabetes Mellitus and Obesity. HLA-typing, clinical, and immunological characterization of youth with type 2 diabetes mellitus phenotype from the German/Austrian DPV database. *Pediatr Diabetes* 2013; 14(8): 562-74. <http://dx.doi.org/10.1111/pedi.12043> PMID: 23627341
- [62] DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 1988; 37(6): 667-87. <http://dx.doi.org/10.2337/diab.37.6.667> PMID: 3289989
- [63] Groop L, Lyssenko V. Genes and type 2 diabetes mellitus. *Curr Diab Rep* 2008; 8(3): 192-7. <http://dx.doi.org/10.1007/s11892-008-0033-y> PMID: 18625115
- [64] Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest* 2000; 106(4): 453-8. <http://dx.doi.org/10.1172/JCI10762> PMID: 10953019
- [65] Eriksson J, Franssila-Kallunki A, Ekstrand A, *et al.* Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 1989; 321(6): 337-43. <http://dx.doi.org/10.1056/NEJM198908103210601> PMID: 2664520
- [66] Weiss R, Dufour S, Taksali SE, *et al.* Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet* 2003; 362(9388): 951-7. [http://dx.doi.org/10.1016/S0140-6736\(03\)14364-4](http://dx.doi.org/10.1016/S0140-6736(03)14364-4) PMID: 14511928
- [67] Bergman RN, Iyer MS. Indirect Regulation of Endogenous Glucose Production by Insulin: The Single Gateway Hypothesis Revisited. *Diabetes* 2017; 66(7): 1742-7. <http://dx.doi.org/10.2337/db16-1320> PMID: 28637826
- [68] Sivitz WI, Yorek MA. Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. *Antioxid Redox Signal* 2010; 12(4): 537-77. <http://dx.doi.org/10.1089/ars.2009.2531> PMID: 19650713
- [69] Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. *Curr Diabetes Rev* 2013; 9(1): 25-53. <http://dx.doi.org/10.2174/157339913804143225> PMID: 22974359
- [70] von Berghe C, Brabant G, Biebermann H, Krude H, Wiegand S. Proinsulin and the proinsulin/insulin ratio in overweight and obese children and adolescents: relation to clinical parameters, insulin resistance, and impaired glucose regulation. *Pediatr Diabetes* 2011; 12(3 Pt 2): 242-9. <http://dx.doi.org/10.1111/j.1399-5448.2010.00734.x> PMID: 21518412
- [71] Roder ME, Dinesen B, Hartling SG, *et al.* Intact proinsulin and beta-cell function in lean and obese subjects with and without type 2 diabetes. *Diabetes Care* 1999; 22(4): 609-14. <http://dx.doi.org/10.2337/diacare.22.4.609> PMID: 10189540
- [72] Gungor N, Bacha F, Saad R, Janosky J, Arslanian S. Youth type 2 diabetes: insulin resistance, beta-cell failure, or both? *Diabetes Care* 2005; 28(3): 638-44. <http://dx.doi.org/10.2337/diacare.28.3.638> PMID: 15735201
- [73] Beck-Nielsen H, Hother-Nielsen O, Staehr P. Is hepatic glucose production increased in type 2 diabetes mellitus? *Curr Diab Rep* 2002; 2(3): 231-6.



- http://dx.doi.org/10.1007/s11892-002-0088-0 PMID: 12643178
- [74] Lin HV, Accili D. Hormonal regulation of hepatic glucose production in health and disease. *Cell Metab* 2011; 14(1): 9-19. http://dx.doi.org/10.1016/j.cmet.2011.06.003 PMID: 21723500
- [75] Godoy-Matos AF. The role of glucagon on type 2 diabetes at a glance. *Diabetol Metab Syndr* 2014; 6(1): 91. http://dx.doi.org/10.1186/1758-5996-6-91 PMID: 25177371
- [76] Umpaichitra V, Bastian W, Taha D, Banerji MA, AvRuskin TW, Castells S. C-peptide and glucagon profiles in minority children with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2001; 86(4): 1605-9. http://dx.doi.org/10.1210/jcem.86.4.7415 PMID: 11297591
- [77] Moon JS, Won KC. Pancreatic  $\alpha$ -Cell Dysfunction in Type 2 Diabetes: Old Kids on the Block. *Diabetes Metab J* 2015; 39(1): 1-9. http://dx.doi.org/10.4093/dmj.2015.39.1.1 PMID: 25729706
- [78] Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol* 2008; 9(5): 367-77. http://dx.doi.org/10.1038/nrm2391 PMID: 18401346
- [79] Stinkens R, Goossens GH, Jocken JW, Blaak EE. Targeting fatty acid metabolism to improve glucose metabolism. *Obes Rev* 2015; 16(9): 715-57. http://dx.doi.org/10.1111/obr.12298 PMID: 26179344
- [80] Titchenell PM, Lazar MA, Birnbaum MJ. Unraveling the Regulation of Hepatic Metabolism by Insulin. *Trends Endocrinol Metab* 2017; 28(7): 497-505. http://dx.doi.org/10.1016/j.tem.2017.03.003 PMID: 28416361
- [81] Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000; 106(4): 473-81. http://dx.doi.org/10.1172/JCI10842 PMID: 10953022
- [82] Boden G. Free fatty acids, insulin resistance, and type 2 diabetes mellitus. *Proc Assoc Am Physicians* 1999; 111(3): 241-8. http://dx.doi.org/10.1046/j.1525-1381.1999.99220.x PMID: 10354364
- [83] Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005; 307(5708): 384-7. http://dx.doi.org/10.1126/science.1104343 PMID: 15662004
- [84] Parish R, Petersen KF. Mitochondrial dysfunction and type 2 diabetes. *Curr Diab Rep* 2005; 5(3): 177-83. http://dx.doi.org/10.1007/s11892-005-0006-3 PMID: 15929863
- [85] Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. *Diabetes* 1997; 46(1): 3-10. http://dx.doi.org/10.2337/diab.46.1.3 PMID: 8971073
- [86] Sinaiko AR, Donahue RP, Jacobs DR Jr, Prineas RJ. Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin, and lipids in young adults. The Minneapolis Children's Blood Pressure Study. *Circulation* 1999; 99(11): 1471-6. http://dx.doi.org/10.1161/01.CIR.99.11.1471 PMID: 10086972
- [87] Tenenbaum A, Klempfner R, Fisman EZ. Hypertriglyceridemia: a too long unfairly neglected major cardiovascular risk factor. *Cardiovasc Diabetol* 2014; 13: 159. http://dx.doi.org/10.1186/s12933-014-0159-y PMID: 25471221
- [88] Gastaldelli A, Cusi K, Pettiti M, *et al.* Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. *Gastroenterology* 2007; 133(2): 496-506. http://dx.doi.org/10.1053/j.gastro.2007.04.068 PMID: 17681171
- [89] Ameer F, Scandiuzzi L, Hasnain S, Kalbacher H, Zaidi N. De novo lipogenesis in health and disease. *Metabolism* 2014; 63(7): 895-902. http://dx.doi.org/10.1016/j.metabol.2014.04.003 PMID: 24814684
- [90] Jensen-Urstad AP, Semenkovich CF. Fatty acid synthase and liver triglyceride metabolism: housekeeper or messenger? *Biochim Biophys Acta* 2012; 1821(5): 747-53. http://dx.doi.org/10.1016/j.bbailip.2011.09.017 PMID: 22009142
- [91] Fon Tacer K, Rozman D. Nonalcoholic Fatty liver disease: focus on lipoprotein and lipid deregulation. *J Lipids* 2011; 2011783976 http://dx.doi.org/10.1155/2011/783976 PMID: 21773052
- [92] Kotronen A, Juurinen L, Tiikkainen M, Vehkavaara S, Yki-Järvinen H. Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. *Gastroenterology* 2008; 135(1): 122-30. http://dx.doi.org/10.1053/j.gastro.2008.03.021 PMID: 18474251
- [93] Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic Fatty liver disease: a pathogenic duo. *Endocr Rev* 2013; 34(1): 84-129. http://dx.doi.org/10.1210/er.2012-1009 PMID: 23238855
- [94] Roth CL, Reinehr T. Roles of gastrointestinal and adipose tissue peptides in childhood obesity and changes after weight loss due to lifestyle intervention. *Arch Pediatr Adolesc Med* 2010; 164(2): 131-8. http://dx.doi.org/10.1001/archpediatrics.2009.265 PMID: 20124141
- [95] Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia* 1998; 41(10): 1241-8. http://dx.doi.org/10.1007/s001250051058 PMID: 9794114
- [96] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; 112(12): 1796-808. http://dx.doi.org/10.1172/JCI200319246 PMID: 14679176
- [97] Lara-Castro C, Garvey WT. Intracellular lipid accumulation in liver and muscle and the insulin resistance syndrome. *Endocrinol Metab Clin North Am* 2008; 37(4): 841-56. http://dx.doi.org/10.1016/j.ecl.2008.09.002 PMID: 19026935
- [98] Cieślak M, Wojtczak A, Cieślak M. Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment. *Acta Biochim Pol* 2015; 62(1): 15-21. http://dx.doi.org/10.18388/abp.2014\_853 PMID: 25781159
- [99] Lean ME, Leslie WS, Barnes AC, *et al.* Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2017. PMID: 29221645
- [100] Goss AM, Goree LL, Ellis AC, *et al.* Effects of diet macronutrient composition on body composition and fat distribution during weight maintenance and weight loss. *Obesity (Silver Spring)* 2013; 21(6): 1139-42. http://dx.doi.org/10.1002/oby.20191 PMID: 23671029
- [101] Goss AM, Chandler-Laney PC, Ovalle F, *et al.* Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. *Metabolism* 2014; 63(10): 1257-64. http://dx.doi.org/10.1016/j.metabol.2014.07.007 PMID: 25125349
- [102] Gower BA, Chandler-Laney PC, Ovalle F, *et al.* Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. *Clin Endocrinol (Oxf)* 2013; 79(4): 550-7. http://dx.doi.org/10.1111/cen.12175 PMID: 23444983
- [103] Mayer SB, Jeffreys AS, Olsen MK, McDuffie JR, Feinglos MN, Yancy WS Jr. Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. *Diabetes Obes Metab* 2014; 16(1): 90-3. http://dx.doi.org/10.1111/dom.12191 PMID: 23911112
- [104] Feinman RD, Pogozelski WK, Astrup A, *et al.* Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition* 2015; 31(1): 1-13. http://dx.doi.org/10.1016/j.nut.2014.06.011 PMID: 25287761
- [105] Chen X, Yang W. Branched-chain amino acids and the association with type 2 diabetes. *J Diabetes Investig* 2015; 6(4): 369-70. http://dx.doi.org/10.1111/jdi.12345 PMID: 26221513
- [106] McCormack SE, Shaham O, McCarthy MA, *et al.* Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. *Pediatr Obes* 2013; 8(1): 52-61. http://dx.doi.org/10.1111/j.2047-6310.2012.00087.x PMID: 22961720
- [107] Tricò D, Prinsen H, Giannini C, *et al.* Elevated  $\alpha$ -hydroxybutyrate and branched-chain amino acid levels predict deterioration of glycaemic control in adolescents. *J Clin Endocrinol Metab* 2017; 102(7): 2473-81. http://dx.doi.org/10.1210/jc.2017-00475 PMID: 28482070
- [108] Gardner CD, Trepanowski JF, Del Gobbo LC, *et al.* Effect of low-fat vs. low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The dietfits randomized clinical trial. *JAMA* 2018; 319(7): 667-79. http://dx.doi.org/10.1001/jama.2018.0245 PMID: 29466592
- [109] Poudel RR. Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. *Indian J Endocrinol Metab* 2013; 17(4): 588-93. http://dx.doi.org/10.4103/2230-8210.113725 PMID: 23961473
- [110] Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev* 2008; 60(4): 470-512.

- <http://dx.doi.org/10.1124/pr.108.000604> PMID: 19074620
- [111] Michaliszyn SF, Mari A, Lee S, *et al.*  $\beta$ -cell function, incretin effect, and incretin hormones in obese youth along the span of glucose tolerance from normal to prediabetes to type 2 diabetes. *Diabetes* 2014; 63(11): 3846-55.  
<http://dx.doi.org/10.2337/db13-1951> PMID: 24947360
- [112] Yagihashi S. Diabetes and pancreas size, does it matter? *J Diabetes Investig* 2017; 8(4): 413-5.  
<http://dx.doi.org/10.1111/jdi.12590> PMID: 27808474
- [113] Macauley M, Percival K, Thelwall PE, Hollingsworth KG, Taylor R. Altered volume, morphology and composition of the pancreas in type 2 diabetes. *PLoS One* 2015; 10(5)e0126825  
<http://dx.doi.org/10.1371/journal.pone.0126825> PMID: 25950180
- [114] Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; 52(1): 102-10.  
<http://dx.doi.org/10.2337/diabetes.52.1.102> PMID: 12502499
- [115] Saisho Y, Butler AE, Meier JJ, *et al.* Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. *Clin Anat* 2007; 20(8): 933-42.  
<http://dx.doi.org/10.1002/ca.20543> PMID: 17879305
- [116] Bacha F, Cheng P, Gal RL, *et al.* For the Pediatric diabetes consortium. Initial presentation of type 2 diabetes in adolescents predicts durability of successful treatment with metformin monotherapy: Insights from the pediatric diabetes consortium t2d registry. *Horm Res Paediatr* 2018; 89(1): 47-55.  
<http://dx.doi.org/10.1159/000481687> PMID: 29131017