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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Omics era in type 2 diabetes: From childhood to adulthood

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Abstract

Parallel to the dramatic rise of pediatric obesity, estimates reported an increased prevalence of type 2 diabetes (T2D) already in childhood. The close relationship between obesity and T2D in children is mainly sustained by insulin resistance (IR). In addition, the cardiometabolic burden of T2D including nonalcoholic fatty liver disease, cardiovascular disease and metabolic syndrome is also strictly related to IR. Although T2D pathophysiology has been largely studied in an attempt to improve therapeutic options, molecular mechanisms are still not fully elucidated. In this perspective, omics approaches (including lipidomics, metabolomics, proteomics and metagenomics) are providing the most attractive therapeutic options for T2D. In particular, distinct both lipids and metabolites are emerging as potential therapeutic tools. Of note, among lipid classes, the pathogenic role of ceramides in T2D context has been supported by several data. Thus, selective changes of ceramides expression might represent innovative therapeutic strategies for T2D treatment. More, distinct metabolomics pathways have been also found to be associated with higher T2D risk, by providing novel potential T2D biomarkers. Taken together, omics data are responsible for the expanding knowledge of T2D pathophysiology, by providing novel insights to improve therapeutic strategies for this tangled disease. We aimed to summarize the most recent evidence in the intriguing field of the omics approaches in T2D both in adults and children.

Key Words: Omics; Diabetes; Children; Adults; Type 2 diabetes

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Core Tip: Type 2 diabetes (T2D) represents an emerging health concern worldwide. Its

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cardiometabolic burden affects both adults and children. Given the alarming rise of pediatric obesity, a high prevalence of T2D has been reported already in childhood. Although lifestyle modifications and metformin represent the first-line therapy for T2D, several drugs are available and others are being studied. In this view, an attractive therapeutic tool derives from omics studies. Based on T2D pathophysiology, these analyses highlighted the role of different lipids and metabolites closely intertwined with insulin signaling pathways as potential biomarkers for T2D, by paving the way for novel treatment strategies.

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INTRODUCTION

Type 2 diabetes (T2D) is a global epidemic with an increasing prevalence both in adults and children[1,2]. Estimates have reported > 450 million T2D adult patients in 2019 with a potential rise to 700 million by the next three decades[2]. In children, the alarming T2D increase has been mainly linked to the concomitant obesity epidemic[3-5]. Recent data from the United States indicate an incidence of almost 5000 new pediatric T2D cases per year[1]. Similarly, an increased overall prevalence of T2D in adolescence has been observed over the past few years and is expected to be quadrupled in the next 40 years[6,7].

According to the American Diabetes Association, T2D criteria included fasting plasma glucose (FPG) ≥ 126 mg/dL or 2-h glucose concentration during an oral glucose tolerance test ≥ 200 mg/dL or hemoglobin A1C $\geq 6.5\%$ [8].

Several factors (*e.g.*, genetic, epigenetic, metabolic and environmental) are involved in the complex pathophysiology of T2D, but insulin resistance (IR) and beta-cell dysfunction are recognized as key pathogenic players[1,4,5,9-12]. As result of various metabolic insults (*e.g.*, oxidative stress, vascular damage and lipotoxicity), different organs and systems (including heart, kidney, brain, liver, eyes and nervous system) are affected[10,11].

In particular, T2D consequences in adults are clustered in macrovascular and microvascular diseases. The former group (including stroke, myocardial infarction and peripheral artery disease) has been closely linked to hyperglycemia, hyperinsulinemia and dyslipidemia, while the latter (*i.e.*, retinopathy, kidney disease and neuropathy) has been related both to proinflammatory and prothrombotic effects of hyperglycemia and to cell lipid content changes[1,10].

The burden of comorbidities in pediatric T2D [including fatty liver, cardiovascular disease (CVD), kidney injury, and metabolic syndrome (MetS)] has been closely intertwined with obesity, representing the most important risk factor for T2D development at this age[1,13-15]. More specifically, IR represents the shared pathogenic feature of the entire spectrum of comorbidities, by underscoring its pivotal role in metabolic derangements[16].

Although several pharmacological options are currently available, lifestyle modifications and metformin remain the first-line therapy in adolescence[17]. In this perspective, new insights for T2D treatment have recently emerging from omics studies[18-21]. Indeed, this intriguing field (including metabolomics, proteomics, genomics and lipidomics) has currently provided evidence for a pathogenic role in several metabolic diseases[22-25].

Despite the large availability of data on T2D pathophysiology, less is known on molecular changes caused by hyperglycemia[26-31]. In an effort to enhance therapeutic strategies for this insidious disease, innovative recent studies focused on the pathophysiological significance of these modifications T2D-related through omics approaches.

We aimed to summarize the most recent evidence in this intriguing field both in children and in adults.

OMICS

As omics branches, different classes including genomics, proteomics, metabolomics and metagenomics provide a refined assessment by examining both quantitative and qualitative biomolecular characteristics.

Recently, a growing body of evidence has supported a pathogenic role of distinct lipid class including sphingolipids (in particular ceramides) for several metabolic disorders such as obesity, MetS, IR, CVD, nonalcoholic fatty liver disease (NAFLD) and T2D both in adults and children. Plasma ceramides levels have been closely linked to glucose homeostasis derangements and NAFLD through insulin signaling pathways impairment.

From a metabolic perspective, these new branches have allowed advances in the understanding of pathophysiology of beta-cell dysfunction leading to T2D development. Besides evidence from experimental models, there is a large amount of data in adult population and a still limited but compelling body of evidence in children.

Animal studies

A large body of evidence regarding omics approaches on T2D has been provided by experimental studies conducted on animal models (Table 1). Chen *et al*[32] investigated the role of lipids in diabetes development and evolution of diabetes using high-fat diet-streptozocin (HFD-STZ) induced diabetes in mice. In particular, the authors demonstrated this role in different organs such as heart, kidney and brain. Cardiac changes expressed as reduction in cardiolipin species with long chains were reported in the atrium and ventricle, while triglyceride (TG) levels were found to be decreased in the ventricle and increased in the atrium[32].

Likewise, renal changes were also demonstrated. Specifically, a reduction of TG species with shorter fatty chains and an increase of the long fatty chain TGs in the medulla were detected. Changes in the renal cortex were similar but involved longer fatty chains than in the medulla, by suggesting a targeted role of the lipidome in different regions of the same organ[32].

Lastly, cerebral change of HFD-STZ mice showed a higher reduction of cardiolipin levels, indicating a loss of mitochondrial function more severe compared to other organs[32].

As a consequence of the expanding knowledge on T2D pathophysiology through omics approaches, a pathogenic role of dyslipidemia (defined as elevated plasma triacylglycerol and cholesteryl esters levels) for microvascular disease development has been reported in animal models[33]. Indeed, Eid *et al*[33] found increased levels of several lipid species in the kidney and nerves and reduced overall lipid content in the retina of an experimental model of diabetic mouse.

Human studies

Omics techniques in human models have allowed identification of novel attractive therapeutic tools for several metabolic disorders including T2D. Indeed, these approaches have provided a better elucidation of the molecular pathogenic changes underpinning T2D and its comorbidities.

Evidence in adults

Most studies performing omics analyses have reported intriguing associations of different lipids and metabolites with T2D in adults (Table 2). Ge *et al*[34] studied the association between FPG levels and single nucleotide polymorphisms (SNPs)[34]; 76 out of 511 participants presented with increased FPG levels and 435 had decreased or fluctuant FPG concentrations. Nine SNPs in five genes (*RPL7AP27*, *SNX30*, *SLC39A12*, *BACE2* and *IGFL2*) were significantly associated with increased FPG levels[34]. Moreover, among the 24 identified glycan peaks (GPs), GPs 3, 8 and 11 showed a positive trend with increased FPG levels, while the opposite was found for GPs 4 and 14[34]. These findings provided evidence for novel potential biomarker for T2D through the combination of candidate SNPs and IgG glycomics[34].

Another study conducted on 1974 healthy subjects aged 50-70 years showed the role of sphingolipids as markers for incident T2D[35]. In fact, during the 6 years' follow-up, 529 participants developed T2D. In particular, 14 sphingolipids (of which 11 newly described) namely ceramides (d18:1/18:1, d18:1/20:0, d18:1/20:1 and d18:1/22:1), saturated sphingomyelins (C34:0, C36:0, C38:0 and C40:0), unsaturated sphingomyelins (C34:1, C36:1 and C42:3), hydroxyl-sphingomyelins (C34:1 and C38:3), and a hexosylceramide (d18:1/20:1), were positively associated with incident T2D[35].

Table 1 Main findings of the omics studies in animal models

Ref.	Experimental design	Main findings
Eid <i>et al</i> [33]	Examination of changes in glucose and lipid metabolism in the kidney, eye and nerve of leptin receptor KO BKS <i>db/db</i> mouse model	Glycolytic genes were uniformly upregulated in kidney and peripheral nerves; glycolytic metabolites were increased in kidney and retina but decreased in the peripheral nerve. Kidney and nerves showed an overall trend towards increased levels of different lipid species, while in the retina lipid content was decreased
Chen <i>et al</i> [32]	Evaluation of the characteristic of lipid species in serum and tissues in a diabetic mouse model fed a high fat diet and treated with streptozocin by using LC/HRMS and MS/MS	Brain and heart showed the largest reduction in cardiolipin levels, while the kidney had more alteration in triacylglycerol levels. Cardiolipin with highly polyunsaturated fatty acyls decreased only in the atrium but not in the ventricle; similarly, renal cortex showed longer fatty acyl chains both for increased and decreased triacylglycerol species than renal medulla
Guillon <i>et al</i> [25]	Systematic review about the role S1P in the development of T2D and obesity	SphK1 KO in rat pancreatic β -cells and in INS-1 cells resulted in both lowered glucose-stimulated insulin secretion and insulin content associated with decreased insulin gene expression. Conversely, SphK1 overexpression restored both insulin synthesis and secretion. HFD-fed SphK1 ko mice also showed a reduction of β -cells size, number and mass due to lipotoxic condition

T2D: Type 2 diabetes; HFD: High fat diet; LC/HRMS: Liquid chromatography high-resolution tandem; MS: Mass spectrometry.

The Weighted Gene Correlation Network Analysis generated five modules containing different species of sphingolipids, of which two clusters including saturated sphingomyelins showed the strongest association with increased T2D risk[35].

Omics approaches have also been used for examining the effect of certain drugs on tissue molecules. Peterson *et al*[36] investigated the effect of fenofibrate treatment on cardiac function in 65 T2D patients subdivided in treated (31 subjects) and placebo (34 subjects) groups. Fenofibrate is a fibric acid derivative, whose active metabolite is responsible for the primary pharmacodynamic drug effects, including reduction in total plasma cholesterol, low density lipoprotein cholesterol, TG, and very low-density lipoprotein concentrations and increase in high-density lipoprotein cholesterol and apolipoprotein AI and AII concentrations[37]. These effects are mediated by the activation of peroxisome proliferator-activated receptor-[36]. No significant changes in body mass index, diabetes control and hemodynamics were observed between the two groups. Fenofibrate treatment decreased plasma C24:0/C16:0 ceramide ratio (likely related to worsening in diastolic function) with slight changes in oxidative stress markers but no effect on inflammation[36]. It also seemed to be linked to diastolic function improvement through lowering TG plasma levels, but systolic or diastolic function did not significantly differ in both groups[36].

In addition, more data using a comprehensive omics approach (including lipidomics, metabolomics, and proteomics) support the close relationship of specific lipid class[38-40] and metabolites[41-44] with the metabolic milieu.

Evidence in children

Because of the pediatric obesity epidemic, an increasing prevalence of T2D in children has been reported over the last few decades[1]. In order to counteract the “diabesity” epidemic, novel therapeutic options are being studied. In this view, as observed in adults, meaningful data are provided by omics also in childhood[45-51] (Table 3).

Among lipid classes, the most interesting findings have been related to ceramides, representing important bioactive lipids belonging to the sphingolipid family produced from a fatty acid and sphingosine or by sphingomyelin hydrolysis affect cell signaling pathways involved in metabolic processes[22,24,28]. To date, these lipids are considered as the major players in IR development, as demonstrated by several works both in adults and children linking ceramides to various cardiometabolic diseases such as obesity, MetS, NAFLD, T2D, CVD and chronic kidney diseases[20,22,24,51].

Lopez *et al*[51] examined the role of ceramides and adiponectin in 28 female adolescents (14 healthy and 14 obese girls with T2D) aged 10–17 years. Higher C 18:0, C22:0 and C20:0 ceramides levels and decreased adiponectin concentrations were found in patients with T2D compared to healthy subjects.

A specific metabolomics signature has been demonstrated in children with metabolic derangements, by underscoring the pathogenic role of different metabolites affecting IR pathways.

Martos-Moreno *et al*[50] studied 100 prepubertal children with obesity (50 female/50 male, 50% IR and 50% non-IR for each group) by performing an oral glucose tolerance test for usual carbohydrate and lipid metabolism determinations. In IR obese children, impairments in the urea cycle, alanine metabolism and the glucose-alanine cycle were detected, suggesting a possible role of mitochondrial

Table 2 Main findings of the omics studies in adults

Ref.	Study design	Population (n)	Main findings
Ge <i>et al</i> [34]	Community-based case-control study	511 healthy adults, mean age 47.9 yr	76 patients had increased FPG and 435 had decreased or fluctuant FPG. Nine SNPs in five genes were significantly associated with increased FPG. Among the 24 glycan peaks identified, GPs 3, 8 and 11 had a positive trend with increased FPG levels, while opposite findings were found for GPs 4 and 14
Peterson <i>et al</i> [36]	Double-blind, randomized, placebo-controlled, parallel design study	65 adults aged 30-65 yr	Fenofibrate treatment lowered C24:0/C16:0 plasma ratio and minimally altered oxidative stress markers and correlated with worse diastolic function. Plasma TG lowering correlated with improvement in diastolic function
Yun <i>et al</i> [35]	Prospective study	1974 adults, aged 50-70 yr	During the 6 yr follow-up, 529 participants developed T2D. 14 sphingolipids (3 reported and 11 novel) were positively associated with incident T2D. WGCNA analysis generated 5 modules, containing different species of sphingolipids; of these, 2 modules containing saturated sphingomyelins showed the strongest association with increased T2D risk
Sun <i>et al</i> [38]	Systematic review	33 studies on the application of metabolomics to disease related-risk. 5 studies on the applications of metabolomics for disease prediction. 5 studies on the applications of metabolomics biomarkers for disease intervention. 8 studies about the integration of genomic and metabolomics data	The first 33 studies find out different metabolites associated with T2D, heart failure, IR and MetS. Studies about the disease prediction demonstrated that some metabolites (amino acids and lipids) were predictive for T2D. Studies about the applications of biomarkers investigated the effect of diet in reducing some risk factors. Studies on the integration of genomic and metabolomics data reported some allele positively associated with high levels of risk metabolites
Misra and Misra [2]	Systematic review	18 studies about heavy metals. 14 studies about persistent organic pollutants and pesticides. 7 studies about drugs and pharmaceuticals. 11 studies about atmospheric pollution	Heavy metals (<i>e.g.</i> , arsenic, lead, selenium and mercury) were positively associated with increased T2D risk. Some pollutants of the POPs and pesticides' family were directly associated with increased risk of developing T2D. Drugs such as antibiotics, antidepressant or antipsychotics were positively associated with increased T2D risk. Long exposure to atmospheric pollutants such as NO ₂ and PM2.5 were directly associated with T2D
Zhang <i>et al</i> [39]	Cohort study	694 patients (491 HIV-infected and 203 HIV-uninfected) aged 35-55 yr	11 lipids species were identified and associated with T2D risk. No association of HIV status with higher T2D risk was found, while ART use was associated with 8 risk lipids (3 decreased-risk lipids and 5 higher-risk lipids)
Wang <i>et al</i> [40]	Systematic review complication	1 study about application of proteomics in T2D. 1 study about the application of metabolomics in T2D. 1 study about the application of metagenomics in T2D	Proteomics analyses on 62 Mexican T2D patients showed 113 proteins related to T2D risk; in particular, 3 of these have been associated with obesity and T2D while 1 was associated with anti-inflammatory pathways. Metabolomics analyses found 33 metabolites strongly related to T2D. Metagenomics analyses reported different gut microbiota profiles between fecal sample of T2D patients and control subjects
Gudmundsdottir <i>et al</i> [41]	Prospective cohort study	2916 European patients (789 diabetic patients and 2127 non diabetic patients at high T2D risk development)	55 modules of coexpressed genes in the whole blood of the nondiabetic cohort were found. These modules were associated with inflammation, fat tissues, glucose tolerance, insulin sensitivity, and C-reactive protein levels, and were also preserved between non-diabetic and newly diagnosed T2D cohort
Gu <i>et al</i> [42]	Observational study	72 patients (30 normal weight, 26 obese and 16 newly T2D diagnosed)	Obese patients showed upregulation of 78 metabolites and downregulation of 111 metabolites than lean subjects. T2D patients showed upregulation of 459 metabolites and downregulation of 166 metabolites compared to obese subjects. Several metabolites, including amino acids and amino acids metabolites, were identified as IR potential biomarkers
Diamanti <i>et al</i> [43]	Cohort study	42 subjects (12 healthy controls, 16 with prediabetes and 14 T2D subjects)	Plasma metabolomics profiling revealed a positive association of hepatic fat content with tyrosine and a negative relationship with lysophosphatidylcholine. Visceral and subcutaneous adipose tissue insulin sensitivity was positively associated with several lysophospholipids, while the opposite was found for branched-chain amino acids. Several metabolites were significantly higher in T2D subjects than normal/prediabetes subjects
Salihovic <i>et al</i> [44]		1424 adult subjects	Three out of 62 identified metabolites were associated with prevalent T2D (mainly lower urine levels of 3-hydroxyundecanoyl-carnitine). In participants without T2D at baseline, 6 metabolites improving T2D prediction were identified

T2D: Type 2 diabetes; FPG: Fasting plasma glucose; SNP: Single nucleotide polymorphism; TG: Triglycerides; IR: Insulin resistance; WGCNA: Weighted

gene coexpression network analysis.

Table 3 Main findings of the omics studies in children

Ref.	Study design	Population (n)	Main findings
Concepcion <i>et al</i> [45]	Cross-sectional study	90 children (30 healthy children, 30 obese children without T2D and 30 obese children with T2D) aged 13-19 yr	In urine samples of T2D patients, 22 metabolites (including succinylaminoimidazole carboxamide riboside (SAICA-riboside), betaine metabolites (betaine and dimethylglycine), branched chain amino acids (valine and leucine) and their direct catabolic derivatives (2-oxoisovaleric acid, 3-methyl-2-oxovaleric acid, 3-hydroxyisobutyrate) and aromatic amino acids (phenylalanine, tyrosine and tryptophan) were significantly associated in obese children. The metabolite pattern in OB and T2D groups differed between urine and plasma, suggesting that urinary BCAAs and their intermediates behaved as a more specific biomarker for T2D, while plasma BCAAs associated with obesity and IR independently of T2D
Perng <i>et al</i> [46]	Cross-sectional study	524 adolescents aged approximately 13 yr, grouped according to both obesity and glucose tolerance status	Five metabolite patterns differed with respect to phenotype: Factor 1 comprised long-chain fatty acids and was lower among non-OW/OB and high MetRisk <i>vs</i> non-OW/OB and low MetRisk. Factors 5 (branched chain amino acids; BCAAs), 8 (diacylglycerols) and 9 (steroid hormones) were highest among OW/OB and high MetRisk. Factor 7 (long-chain acylcarnitines) was higher among non-OWOB and high MetRisk and lower among OW/OB and low MetRisk
Gawlik <i>et al</i> [47]	Observational study	87 obese children divided in 2 groups (IR and Non-IR children) aged 8.5-17.9 yr old	31 steroid metabolites were quantified by GC-MS. IR was diagnosed in 20 (23%) of the examined patients. The steroidal IR signature was characterized by high adrenal androgens, glucocorticoids, and mineralocorticoid metabolites, higher 5 α -reductase and 21-hydroxylase activity, and lower 11 β HSD1 activity
Müllner <i>et al</i> [48]	Cross sectional study	81 adolescents aged > 10 yr, stratified into four groups based on BMI (lean <i>vs</i> obese), insulin responses (normal)	Two groups of metabolites were identified: (1) Metabolites associated with insulin response level: adolescents with HI (groups 3-4) had higher concentrations of BCAAs and tyrosine, and lower concentrations of serine, glycine, myo-inositol and dimethylsulfone, than adolescents with NI (groups 1-2); and (2) Metabolites associated with obesity status: obese adolescents (groups 2-4) had higher concentrations of acetylcarnitine, alanine, pyruvate and glutamate, and lower concentrations of acetate, than lean adolescents (group 1)
Mastrangelo <i>et al</i> [49]	Observational study	60 prepubertal obese children (30 girls/30 boys, 50% IR and 50% non-IR in each group, but with similar BMI)	47 metabolites out of 818 compounds were found to differ significantly between obese children with and without IR. Bile acids exhibit the greatest changes. The majority of metabolites differing between groups were lysophospholipids (15) and amino acids (17), indicating inflammation and central carbon metabolism as the most altered processes in impaired insulin signaling. Multivariate analysis (OPLS-DA models) showed subtle differences between groups that were magnified when females were analyzed alone
Martos-Moreno <i>et al</i> [50]	Observational study	100 prepubertal obese children (50 girls/50 boys, 50% IR and 50% non-IR in each group)	Twenty-three metabolite sets were enriched in the serum metabolome of IR obese children. The urea cycle, alanine metabolism and glucose-alanine cycle were the most significantly enriched pathways. The high correlation between metabolites related to fatty acid oxidation and amino acids (mainly branched chain and aromatic amino acids) pointed to the possible contribution of mitochondrial dysfunction in IR. The degree of BMI-standard deviation score excess did not correlate with any of the studied metabolomics components. Combination of leptin and alanine showed a high IR discrimination value in the whole cohort in both sexes. However, the specific metabolite/adipokine combinations with highest sensitivity were different between the sexes
Lopez <i>et al</i> [51]	Cross sectional study	28 children (14 obese female subjects with T2D and 14 lean healthy controls) aged 10-17 yr	Children with T2D had higher concentrations of C22:0 and C20:0 ceramides, with a 2-fold increase in C18:0 ceramide and C24:1 dihydroceramide. C22:0, C20:0 and C18:0 ceramide correlated with decreased adiponectin concentrations, increased HOMA-IR, BMI-SDS, triglyceride and fasting blood glucose concentrations. Plasma levels of C18:0, C20:0 and C22:0 ceramide, as well as C24:1 dihydroceramide were elevated in T2D obese female children and adolescents, probably due to tissue IR and low adiponectin levels

T2D: Type 2 diabetes; OB: Obesity; BMI: Body mass index; IR: Insulin resistance; GC-MS: Gas chromatography-mass spectrometry; HOMA-IR: Homeostatic model assessment for insulin resistance; MetRisk: Metabolic risk; 11 β HSD1: 11 β -Hydroxysteroid dehydrogenase type 1; OPLS-DA: Orthogonal partial least squares discriminant analysis.

dysfunction in IR[50]. Collectively, these findings supported the potential application of metabolomics analysis in clinical practice as a noninvasive tool to identify children at risk [50].

In this framework, a role of distinct lipid classes as potential mediators or biomarkers for several metabolic diseases has been widely recognized, but the putative pathophysiological mechanisms underpinning these associations are currently not fully elucidated. Although still limited, pediatric reports in this field are growing and promising.

CONCLUSION

The rising prevalence of the diabetes epidemic has highlighted the urgent need for more effective both prevention and treatment strategies. In this view, the growing knowledge regarding omics pathways affected by insulin signaling has favored the identification of novel potential biomarkers for this alarming epidemic.

Distinct metabolomics and lipidomics pathways have been recently linked to obesity, IR and T2D not only in adults but also in children, by allowing us to expand knowledge about the pathophysiology of several cardiometabolic diseases.

Given the unfavorable prognostic role of metabolic derangements in childhood, a better understanding, such as with omics profiles, of the pathophysiological mechanisms underlying beta-cell dysfunction is crucial. Findings from these studies are providing new insights into the intriguing field of molecular pathways related to IR as a predisposing factor for T2D. Therefore, novel attractive tools are emerging as potential therapeutic agents to counteract the risk of T2D and its related cardiometabolic burden already in childhood[31,33,34].

In particular, lipidomic profiling accompanied by experimental studies using pharmacological reagents to alter synthesis or metabolism of certain lipids, has given additional insights into mechanisms governing lipotoxicity and disease progression, by providing evidence about a role in several crucial cellular responses (*e.g.*, apoptosis, cell cycle and autophagy).

Recently, there has been significant progress in the understanding of the processes of insulin action and molecular defects determining IR, but many gaps according to the pathophysiology of metabolic disorders remain. Published data from studies conducted both on animals and humans have revealed a role for sphingolipids and metabolites in IR in different tissues such as skeletal muscle, liver and adipose tissue.

Among lipid classes, ceramides have gained remarkable attention as the major suspects in the development of IR. Therefore, changes in ceramide generation may become a desired therapeutic target, as shown in rodent models.

Further research is needed to identify the emerging role of both lipids and metabolites in the pathogenesis of cardiometabolic diseases in children in an attempt to provide novel clinical tools with potential therapeutic implications. Findings from the innovative omics era might pave the way for a noninvasive approach of personalized medicine for patients with a greater intrinsic cardiometabolic risk.

REFERENCES

- 1 **Castorani V**, Polidori N, Giannini C, Blasetti A, Chiarelli F. Insulin resistance and type 2 diabetes in children. *Ann Pediatr Endocrinol Metab* 2020; **25**: 217-226 [PMID: 33401880 DOI: 10.6065/apem.2040090.045]
- 2 **Misra BB**, Misra A. The chemical exposome of type 2 diabetes mellitus: Opportunities and challenges in the omics era. *Diabetes Metab Syndr* 2020; **14**: 23-38 [PMID: 31838434 DOI: 10.1016/j.dsx.2019.12.001]
- 3 **Morrison JA**, Glueck CJ, Horn PS, Wang P. Childhood predictors of adult type 2 diabetes at 9- and 26-year follow-ups. *Arch Pediatr Adolesc Med* 2010; **164**: 53-60 [PMID: 20048242 DOI: 10.1001/archpediatrics.2009.228]
- 4 **Kim G**, Caprio S. Diabetes and insulin resistance in pediatric obesity. *Pediatr Clin North Am* 2011; **58**: 1355-1361, ix [PMID: 22093855 DOI: 10.1016/j.pcl.2011.09.002]
- 5 **Hagman E**, Besor O, Hershkop K, Santoro N, Pierpont B, Mata M, Caprio S, Weiss R. Relation of the degree of obesity in childhood to adipose tissue insulin resistance. *Acta Diabetol* 2019; **56**: 219-226 [PMID: 30637483 DOI: 10.1007/s00592-018-01285-3]
- 6 **Liu LL**, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, Dabelea D, Hamman R, Waitzfelder B, Kahn HS; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. *Pediatr Diabetes* 2010; **11**: 4-11 [PMID: 19473302 DOI: 10.1111/j.1399-5448.2009.00519.x]
- 7 **Andes LJ**, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. *JAMA Pediatr* 2020; **174**: e194498 [PMID: 31790544 DOI: 10.1001/jamapediatrics.2019.4498]
- 8 **American Diabetes Association**. 13. Children and Adolescents: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020; **43**: S163-S182 [PMID: 31862756 DOI: 10.2337/dc20-S013]
- 9 **Copeland KC**, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K, Kaufman FR, Linder B, Marcovina S, McGuigan P, Pyle L, Tamborlane W, Willi S; 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**: 159-167 [PMID: 20962021 DOI: 10.1210/jc.2010-1642]
- 10 **Oikonomou E**, Tsioufis C, Tousoulis D. Diabetes mellitus: a primary metabolic disturbance. Metabolomics underlying vascular responses to stress and ischemia? *Clin Sci (Lond)* 2021; **135**: 589-

- 591 [PMID: [33565585](#) DOI: [10.1042/CS20201299](#)]
- 11 **Valaiyapathi B**, Gower B, Ashraf AP. Pathophysiology of Type 2 Diabetes in Children and Adolescents. *Curr Diabetes Rev* 2020; **16**: 220-229 [PMID: [29879890](#) DOI: [10.2174/1573399814666180608074510](#)]
 - 12 **Rughani A**, Friedman JE, Tryggstad JB. Type 2 Diabetes in Youth: the Role of Early Life Exposures. *Curr Diab Rep* 2020; **20**: 45 [PMID: [32767148](#) DOI: [10.1007/s11892-020-01328-6](#)]
 - 13 **Morandi A**, Di Sessa A, Zusi C, Umano GR, El Mazloum D, Fornari E, Miraglia Del Giudice E, Targher G, Maffei C. Nonalcoholic Fatty Liver Disease and Estimated Insulin Resistance in Obese Youth: A Mendelian Randomization Analysis. *J Clin Endocrinol Metab* 2020; **105** [PMID: [32841326](#) DOI: [10.1210/clinem/dgaa583](#)]
 - 14 **Di Bonito P**, Valerio G, Licenziati MR, Miraglia Del Giudice E, Baroni MG, Morandi A, Maffei C, Campana G, Spreghini MR, Di Sessa A, Morino G, Crinò A, Chiesa C, Pacifico L, Manco M. High uric acid, reduced glomerular filtration rate and non-alcoholic fatty liver in young people with obesity. *J Endocrinol Invest* 2020; **43**: 461-468 [PMID: [31637675](#) DOI: [10.1007/s40618-019-01130-6](#)]
 - 15 **Tricò D**, Di Sessa A, Caprio S, Chalasani N, Liu W, Liang T, Graf J, Herzog RI, Johnson CD, Umano GR, Feldstein AE, Santoro N. Oxidized Derivatives of Linoleic Acid in Pediatric Metabolic Syndrome: Is Their Pathogenic Role Modulated by the Genetic Background and the Gut Microbiota? *Antioxid Redox Signal* 2019; **30**: 241-250 [PMID: [28279074](#) DOI: [10.1089/ars.2017.7049](#)]
 - 16 **Marzuillo P**, Di Sessa A, Guarino S, Capalbo D, Umano GR, Pedullà M, La Manna A, Cirillo G, Miraglia Del Giudice E. Nonalcoholic fatty liver disease and eGFR levels could be linked by the PNPLA3 I148M polymorphism in children with obesity. *Pediatr Obes* 2019; **14**: e12539 [PMID: [31184438](#) DOI: [10.1111/ijpo.12539](#)]
 - 17 **Singhal S**, Kumar S. Current Perspectives on Management of Type 2 Diabetes in Youth. *Children (Basel)* 2021; **8** [PMID: [33435250](#) DOI: [10.3390/children8010037](#)]
 - 18 **Masarone M**, Troisi J, Aglitti A, Torre P, Colucci A, Dallio M, Federico A, Balsano C, Persico M. Untargeted metabolomics as a diagnostic tool in NAFLD: discrimination of steatosis, steatohepatitis and cirrhosis. *Metabolomics* 2021; **17**: 12 [PMID: [33458794](#) DOI: [10.1007/s11306-020-01756-1](#)]
 - 19 **Kartoli S**, Kostara CE, Tsimihodimos V, Bairaktari ET, Christodoulou DK. Lipidomics in non-alcoholic fatty liver disease. *World J Hepatol* 2020; **12**: 436-450 [PMID: [32952872](#) DOI: [10.4254/wjh.v12.i8.436](#)]
 - 20 **Apostolopoulou M**, Gordillo R, Gancheva S, Strassburger K, Herder C, Esposito I, Schlensak M, Scherer PE, Roden M. Role of ceramide-to-dihydroceramide ratios for insulin resistance and non-alcoholic fatty liver disease in humans. *BMJ Open Diabetes Res Care* 2020; **8** [PMID: [33219119](#) DOI: [10.1136/bmjdc-2020-001860](#)]
 - 21 **McHenry SA**, Davidson NO. Ceramide Salvage, Gut Mucosal Immunoglobulin A Signaling, and Diet-Induced NASH. *Hepatology* 2021; **73**: 884-886 [PMID: [33449367](#) DOI: [10.1002/hep.31707](#)]
 - 22 **Chaurasia B**, Summers SA. Ceramides in Metabolism: Key Lipotoxic Players. *Annu Rev Physiol* 2021; **83**: 303-330 [PMID: [33158378](#) DOI: [10.1146/annurev-physiol-031620-093815](#)]
 - 23 **Lair B**, Laurens C, Van Den Bosch B, Moro C. Novel Insights and Mechanisms of Lipotoxicity-Driven Insulin Resistance. *Int J Mol Sci* 2020; **21** [PMID: [32887221](#) DOI: [10.3390/ijms21176358](#)]
 - 24 **Raichur S**. Ceramide Synthases Are Attractive Drug Targets for Treating Metabolic Diseases. *Front Endocrinol (Lausanne)* 2020; **11**: 483 [PMID: [32849276](#) DOI: [10.3389/fendo.2020.00483](#)]
 - 25 **Guitton J**, Bandet CL, Mariko ML, Tan-Chen S, Bourron O, Benomar Y, Hajdich E, Le Stunff H. Sphingosine-1-Phosphate Metabolism in the Regulation of Obesity/Type 2 Diabetes. *Cells* 2020; **9** [PMID: [32668665](#) DOI: [10.3390/cells9071682](#)]
 - 26 **Zhao X**, Gang X, Liu Y, Sun C, Han Q, Wang G. Using Metabolomic Profiles as Biomarkers for Insulin Resistance in Childhood Obesity: A Systematic Review. *J Diabetes Res* 2016; **2016**: 8160545 [PMID: [27517054](#) DOI: [10.1155/2016/8160545](#)]
 - 27 **Rupérez FJ**, Martos-Moreno GÁ, Chamoso-Sánchez D, Barbas C, Argente J. Insulin Resistance in Obese Children: What Can Metabolomics and Adipokine Modelling Contribute? *Nutrients* 2020; **12** [PMID: [33137934](#) DOI: [10.3390/nu12113310](#)]
 - 28 **Summers SA**, Chaurasia B, Holland WL. Metabolic Messengers: ceramides. *Nat Metab* 2019; **1**: 1051-1058 [PMID: [32694860](#) DOI: [10.1038/s42255-019-0134-8](#)]
 - 29 **Field BC**, Gordillo R, Scherer PE. The Role of Ceramides in Diabetes and Cardiovascular Disease Regulation of Ceramides by Adipokines. *Front Endocrinol (Lausanne)* 2020; **11**: 569250 [PMID: [33133017](#) DOI: [10.3389/fendo.2020.569250](#)]
 - 30 **Tahir UA**, Gerszten RE. Omics and Cardiometabolic Disease Risk Prediction. *Annu Rev Med* 2020; **71**: 163-175 [PMID: [31986080](#) DOI: [10.1146/annurev-med-042418-010924](#)]
 - 31 **Mandal N**, Gramberg R, Mondal K, Basu SK, Tahia F, Dagogo-Jack S. Role of ceramides in the pathogenesis of diabetes mellitus and its complications. *J Diabetes Complications* 2021; **35**: 107734 [PMID: [33268241](#) DOI: [10.1016/j.jdiacomp.2020.107734](#)]
 - 32 **Chen Z**, Liang Q, Wu Y, Gao Z, Kobayashi S, Patel J, Li C, Cai F, Zhang Y, Liang C, Chiba H, Hui SP. Comprehensive lipidomic profiling in serum and multiple tissues from a mouse model of diabetes. *Metabolomics* 2020; **16**: 115 [PMID: [33067714](#) DOI: [10.1007/s11306-020-01732-9](#)]
 - 33 **Eid S**, Sas KM, Abcouwer SF, Feldman EL, Gardner TW, Pennathur S, Fort PE. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* 2019; **62**: 1539-1549 [PMID: [31346658](#) DOI: [10.1007/s00125-019-4959-1](#)]
 - 34 **Ge S**, Wang Y, Song M, Li X, Yu X, Wang H, Wang J, Zeng Q, Wang W. Type 2 Diabetes Mellitus:

- Integrative Analysis of Multiomics Data for Biomarker Discovery. *OMICS* 2018; **22**: 514-523 [PMID: 30004843 DOI: 10.1089/omi.2018.0053]
- 35 **Yun H**, Sun L, Wu Q, Zong G, Qi Q, Li H, Zheng H, Zeng R, Liang L, Lin X. Associations among circulating sphingolipids, β -cell function, and risk of developing type 2 diabetes: A population-based cohort study in China. *PLoS Med* 2020; **17**: e1003451 [PMID: 33296380 DOI: 10.1371/journal.pmed.1003451]
 - 36 **Peterson LR**, Jiang X, Chen L, Goldberg AC, Farmer MS, Ory DS, Schaffer JE. Alterations in plasma triglycerides and ceramides: links with cardiac function in humans with type 2 diabetes. *J Lipid Res* 2020; **61**: 1065-1074 [PMID: 32393551 DOI: 10.1194/jlr.RA120000669]
 - 37 **Guay DR**. Update on fenofibrate. *Cardiovasc Drug Rev* 2002; **20**: 281-302 [PMID: 12481201 DOI: 10.1111/j.1527-3466.2002.tb00098.x]
 - 38 **Sun L**, Li H, Lin X. Linking of metabolomic biomarkers with cardiometabolic health in Chinese population. *J Diabetes* 2019; **11**: 280-291 [PMID: 30239137 DOI: 10.1111/1753-0407.12858]
 - 39 **Zhang E**, Chai JC, Deik AA, Hua S, Sharma A, Schneider MF, Gustafson D, Hanna DB, Lake JE, Rubin LH, Post WS, Anastos K, Brown T, Clish CB, Kaplan RC, Qi Q. Plasma Lipidomic Profiles and Risk of Diabetes: 2 Prospective Cohorts of HIV-Infected and HIV-Uninfected Individuals. *J Clin Endocrinol Metab* 2021; **106**: 999-1010 [PMID: 33420793 DOI: 10.1210/clinem/dgab011]
 - 40 **Wang N**, Zhu F, Chen L, Chen K. Proteomics, metabolomics and metagenomics for type 2 diabetes and its complications. *Life Sci* 2018; **212**: 194-202 [PMID: 30243649 DOI: 10.1016/j.lfs.2018.09.035]
 - 41 **Gudmundsdottir V**, Pedersen HK, Mazzoni G, Allin KH, Artati A, Beulens JW, Banasik K, Brorsson C, Cederberg H, Chabanova E, De Masi F, Elders PJ, Forgie I, Giordano GN, Grallert H, Gupta R, Haid M, Hansen T, Hansen TH, Hattersley AT, Heggie A, Hong MG, Jones AG, Koivula R, Kokkola T, Laakso M, Longreen P, Mahajan A, Mari A, McDonald TJ, McEvoy D, Musholt PB, Pavo I, Prehn C, Ruetten H, Ridderstråle M, Rutters F, Sharma S, Sliker RC, Syed A, Tajes JF, Thomas CE, Thomsen HS, Vangipurapu J, Vestergaard H, Viñuela A, Wesolowska-Andersen A, Walker M, Adamski J, Schwenk JM, McCarthy MI, Pearson E, Dermitzakis E, Franks PW, Pedersen O, Brunak S. Whole blood co-expression modules associate with metabolic traits and type 2 diabetes: an IMI-DIRECT study. *Genome Med* 2020; **12**: 109 [PMID: 33261667 DOI: 10.1186/s13073-020-00806-6]
 - 42 **Gu X**, Al Dubayee M, Alshahrani A, Masood A, Benabdelkamel H, Zahra M, Li L, Abdel Rahman AM, Aljada A. Distinctive Metabolomics Patterns Associated With Insulin Resistance and Type 2 Diabetes Mellitus. *Front Mol Biosci* 2020; **7**: 609806 [PMID: 33381523 DOI: 10.3389/fmolb.2020.609806]
 - 43 **Diamanti K**, Visvanathar R, Pereira MJ, Cavalli M, Pan G, Kumar C, Skrtic S, Risérus U, Eriksson JW, Kullberg J, Komorowski J, Wadelius C, Ahlström H. Integration of whole-body [18 F]FDG PET/MRI with non-targeted metabolomics can provide new insights on tissue-specific insulin resistance in type 2 diabetes. *Sci Rep* 2020; **10**: 8343 [PMID: 32433479 DOI: 10.1038/s41598-020-64524-0]
 - 44 **Salihovic S**, Broeckling CD, Ganna A, Prenni JE, Sundström J, Berne C, Lind L, Ingelsson E, Fall T, Årnlöv J, Nowak C. Non-targeted urine metabolomics and associations with prevalent and incident type 2 diabetes. *Sci Rep* 2020; **10**: 16474 [PMID: 33020500 DOI: 10.1038/s41598-020-72456-y]
 - 45 **Concepcion J**, Chen K, Saito R, Gangaiti J, Mendez E, Nikita ME, Barshop BA, Natarajan L, Sharma K, Kim JJ. Identification of pathognomonic purine synthesis biomarkers by metabolomic profiling of adolescents with obesity and type 2 diabetes. *PLoS One* 2020; **15**: e0234970 [PMID: 32589682 DOI: 10.1371/journal.pone.0234970]
 - 46 **Perng W**, Rifas-Shiman SL, Sordillo J, Hivert MF, Oken E. Metabolomic Profiles of Overweight/Obesity Phenotypes During Adolescence: A Cross-Sectional Study in Project Viva. *Obesity (Silver Spring)* 2020; **28**: 379-387 [PMID: 31876390 DOI: 10.1002/oby.22694]
 - 47 **Gawlik AM**, Shmoish M, Hartmann MF, Wudy SA, Hochberg Z. Steroid Metabolomic Signature of Insulin Resistance in Childhood Obesity. *Diabetes Care* 2020; **43**: 405-410 [PMID: 31727688 DOI: 10.2337/dc19-1189]
 - 48 **Müllner E**, Röhnisch HE, von Brömssen C, Moazzami AA. Metabolomics analysis reveals altered metabolites in lean compared with obese adolescents and additional metabolic shifts associated with hyperinsulinaemia and insulin resistance in obese adolescents: a cross-sectional study. *Metabolomics* 2021; **17**: 11 [PMID: 33438144 DOI: 10.1007/s11306-020-01759-y]
 - 49 **Mastrangelo A**, Martos-Moreno GÁ, García A, Barrios V, Rupérez FJ, Chowen JA, Barbas C, Argente J. Insulin resistance in prepubertal obese children correlates with sex-dependent early onset metabolomic alterations. *Int J Obes (Lond)* 2016; **40**: 1494-1502 [PMID: 27163744 DOI: 10.1038/ijo.2016.92]
 - 50 **Martos-Moreno GÁ**, Mastrangelo A, Barrios V, García A, Chowen JA, Rupérez FJ, Barbas C, Argente J. Metabolomics allows the discrimination of the pathophysiological relevance of hyperinsulinism in obese prepubertal children. *Int J Obes (Lond)* 2017; **41**: 1473-1480 [PMID: 28588306 DOI: 10.1038/ijo.2017.137]
 - 51 **Lopez X**, Goldfine AB, Holland WL, Gordillo R, Scherer PE. Plasma ceramides are elevated in female children and adolescents with type 2 diabetes. *J Pediatr Endocrinol Metab* 2013; **26**: 995-998 [PMID: 23612696 DOI: 10.1515/jpem-2012-0407]



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