

Endothelial impairment evaluation by peripheral arterial tonometry in pediatric endocrinopathies: A narrative review

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Abstract

Endothelial dysfunction (ED) is characterized by an imbalance between vasodilator and vasoconstriction agents. Several pathological conditions clinically diagnosed in childhood and adolescence are characterized by ED and increased risk for early development of microangiopathic and macroangiopathic impairment, in particular type 1 diabetes mellitus (T1DM), T2DM, obesity, metabolic syndrome and pituitary dysfunction associated to various endocrinopathies. More recently insulin resistance following chemotherapy or radiotherapy for tumors, bone marrow transplantation for hematological malignancies (*i.e.*, cancer survivors), or immunosuppressive treatment for solid organ transplantation has been observed. Assessment of ED by means of non-invasive techniques is the gold standard for early ED detection before clinical manifestation. It is aimed to recognize patients at risk and to avoid the development and progression of more serious illnesses. Reactive hyperemia-peripheral artery tonometry is a noninvasive technique to assess peripheral endothelial function by measuring modifications in digital pulse volume during reactive hyperemia, and represents a non-invasive, reproducible and operator-independent tool able to detect precocious ED. This narrative review aimed to provide an overview of the most important papers regarding ED detection by EndoPat 2000 in children and adolescents with different endocrine diseases. A comprehensive search of English language articles was performed in the MEDLINE database without using other search filters except the publication interval between 2005 and 2020.

Key Words: Pediatric diabetes mellitus; Pediatric endocrinopathies; Metabolic syndrome; Cancer survivors; Endothelial dysfunction; Peripheral artery tonometry

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Core Tip: This narrative review highlights the use of a non-invasive, reproducible and non-operator dependent tool aimed to precocious detection of endothelial dysfunction in pediatric patients affected by several endocrine diseases, characterized by the risk of vascular impairment. The review also reports a summary of the most important published papers related to the topic.

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INTRODUCTION

Vascular endothelium

Vascular endothelium (VE) is located on the luminal surface of blood vessels and represents a selective, permeable and protective barrier between bloodstream and vascular wall. VE plays several important physiological, paracrine, endocrine and autocrine functions, mainly to assure normal blood fluidity and flow, and to hinder the entry of microbes and other harmful entities, in order to maintain cardiovascular homeostasis. VE also regulates vascular permeability and smooth muscle cell migration, fibrinolysis and thrombosis, platelet and leukocyte adhesion, angiogenesis and vascular tone[1]. Healthy endothelium has also anti-inflammatory properties due to its capability of reaction against hemodynamic changes by production of numerous vasoactive molecules, mainly nitric oxide and prostacyclin[2].

Endothelial dysfunction (ED) is the consequence of mechanical stimuli, like increased endoluminal pressure and shear stress, or metabolic factors like hormones and vasoactive agents. ED is characterized by an imbalance between vasodilator and vasoconstriction agents and is followed by the release of substances aimed to regulate hemostasis, vasomotor activity and inflammation[3]. Moreover damaged endothelium produces agents stimulating either thrombosis, like plasminogen activator inhibitors and von Willebrand factor, and inflammation, like several adhesion molecules, interleukin-6 and ultrasensitive C-reactive protein. ED is one of the most important predictive and pathogenetic mechanism of a broad spectrum of life-threatening conditions, in particular cardiovascular diseases, and represents the primary causative agent of atherosclerosis[4].

Several pathological conditions clinically diagnosed in childhood and adolescence are characterized by ED and increased risk for early development of microangiopathic and macroangiopathic impairment, in particular type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome (MS), and pituitary dysfunction associated to various endocrinopathies. More recently insulin resistance following chemotherapy or radiotherapy for tumors, bone marrow transplantation for hematological malignancies (*i.e.* cancer survivors) or immunosuppressive treatment for or solid organ transplantation has been observed. A new entity, characterized by insulin resistance and type 2 diabetes has been recently defined as new onset diabetes after transplantation (NODAT)[5-16].

In T1DM, chronic hyperglycemia and, more recently defined, glycemic variability impair endothelium function through different mechanisms: oxidative stress, polyol pathway activity, free-radical accumulation, non enzymatic glycosylation of protein, free-radical accumulation[17,18]. All these mechanisms act in different ways and are responsible for the development of various degrees of diabetic microangiopathy, like retinopathy, nephropathy and peripheral neuropathy[19-21]. Thanks to intensive insulin therapy protocols since diagnosis and advances in technological instruments for T1DM management, clinically evident microangiopathy in children and adolescents is almost rarely encountered; on the other hand, subclinical signs of precocious ED can be detected in adolescents, especially in case of poor degree of metabolic control[22,23].

As regards T2DM, obesity, metabolic syndrome and NODAT, insulin resistance (IR) and its metabolic consequences are the most important causative factors of ED. In particular, obesity, insulin resistance and sedentary lifestyle are the main responsible of different co-morbidities related to so called metabolic syndrome, a proinflammatory state that negatively affects endothelial function and characterized by dyslipidemia, hyperuricemia, hypertension[9,24,25].

While in T1DM microangiopathic damage develops during the natural course of the disease, in newly-diagnosed adolescents with T2DM microangiopathic complications, especially nephropathy, have been reported[26]. The early damage negatively affects quality of life and is responsible for morbidity and mortality even at young age[27,28]. In particular, diabetic kidney disease in youth-onset T2DM is reported as a consequence of lower insulin sensitivity, a condition requiring more O₂ consumption and responsible for increased resistance in efferent arterioles[29].

Improved survival rates in childhood cancer, during the past few decades, have increased the population of survivors. Recent estimates allow to hope that in the general population, one every 500-1000 persons will be a childhood long-term cancer survivor. Young cancer survivors and patients who underwent hematopoietic cell transplantation in childhood are at increased risk of MS and cardiovascular disease[30-33]. Total body irradiation, chemotherapy and immunosuppressive agents are causative factors for insulin resistance[33].

Cardiovascular diseases are the most common cause of premature death in Western countries, and in long-term cancer survivors heart diseases are 5-10 times more common than in their siblings[33]. The population of survivors is increasing over time and with it there is the need for a greater understanding of cardiovascular toxicity, which is an overlap of mechanisms directly related to cancer and late effects of oncological therapies[34].

ED may be the first step in the pathogenesis of chronic conditions, such as atherosclerosis, which leads to cardiovascular system disorders including coronary heart disease, hemorrhagic or ischemic stroke, peripheral arterial disease and venous thromboembolism. The major risk factors of endothelial impairment are high-dose chemotherapy with anthracyclines, alkylating agents, vinca alkaloids and total body radiation, especially in younger age. Cancer therapeutic agents may damage endothelial cells and the delicate balance between vasodilating and vasoconstricting substances produced by and acting on endothelial cells. Radiotherapy increases damage of endothelial cells and arterial stiffness through the loss of elastic matrix and the alteration of microvascular structure[30-34].

ED DETECTION

Early ED detection before clinical manifestation is the most important preventive measure, aimed to recognize patients at risk and to avoid the development and progression of more serious illnesses.

Several serum inflammatory markers are available to detect ED, including pro-inflammatory cytokines, like TNF-alpha, IL-1, IL-6, IL-8, IFN-gamma, pigment epithelium derived factors, adipocyte-specific fatty acid-binding protein, lipocalin-2, resistin[4,35,36]. Insulin resistance is associated by a global inflammatory status, characterized in the majority of cases by positivity of several inflammatory markers and is responsible for endothelial impairment leading to angiopathy. At present none of these markers has a prognostic value, and their use in clinical practice remains speculative. Moreover, inflammatory markers detection requires specific laboratories and equipments.

Assessment of ED by means of non-invasive techniques is the gold standard of its detection, and several methods for research purposes have been developed, otherwise their operator dependency and complexity preclude wide use in clinical practice[37].

In particular, reproducibility of a medical test is the consequence of its low intrinsic variability and represents the gold standard for the meaningfulness of the method. Reproducibility depends on the test itself, i.e. operator dependency accuracy of the instrument, and the variability linked to human physiology. For ED detection reproducibility is an important issue, since endothelial function is extremely variable and labile both intra- and inter-subject[38].

To this purpose several diagnostic methods have been developed, based on the following principles: (1) Specific stimuli determine release of NO from VE to mediate its relaxation; and (2) Test measuring ED in different vascular beds. Endothelial vasomotor testing performed in the coronary vascular bed by coronarangiography

and intracoronary Doppler is the gold standard, however, its invasiveness can raise ethical concerns and is impracticable in research studies[39]. Therefore, alternative vasomotor testing have been proposed in the peripheral circulation, especially in forearm vessels.

Reactive hyperemia-peripheral artery tonometry (RH-PAT) is a non invasive technique to assess peripheral endothelial function by measuring modifications in digital pulse volume during reactive hyperemia, and represents a non-invasive, reproducible and operator-independent tool able to detect precocious ED[40]. Flow mediated dilation has been applied both in adults and adolescents and requires an ultrasound assessment of brachial artery diameter before and after raised shear stress [41,42]. Operator training is required and results may be invalidated by inter-observer variability.

A new automated and less operator-dependent method, named Endo Peripheral Artery Tonometry 2000 (EndoPAT) has been proposed by Itamar Ltd[43]. EndoPAT records endothelium-mediated changes in the digital pulse waveform (PAT signal) using a pair of new modified plethysmographic probes placed on the finger index of each hand[43]. Endothelium-mediated variations of the PAT signal are triggered by inducing a downstream hyperemic response. Hyperemia is elicited by blood flow occlusion through the brachial artery for 5 min using an inflatable cuff on one hand. The response to reactive hyperemia is automatically calculated by the system (Axtec). A PAT ratio is obtained analyzing the pre- and post-occlusion values, and values are normalized to measurements from the contralateral site, considered as control for non-endothelial dependent systemic effects[38] (Figure 1).

To test prospectively the reproducibility and feasibility of EndoPAT, 30 healthy adolescents aged 13 to 19 years were evaluated on 2 different days[38]. The authors concluded that the EndoPAT technique was well tolerated and had excellent reproducibility. On the other hand several factors, mainly pubertal development, may affect microvascular function. To this purpose, Bhargoo *et al*[44] reported that enhancement of the PAT index was positively related to Tanner Stage, probably due to sex steroids influence. Similarly, another study conducted in 94 healthy children and adolescents aimed to evaluate microcirculation by reactive hyperemic index (RHI) reported a positive correlation between RHI and Tanner Stage, age, height, body mass index (BMI), systolic blood pressure values[45]. Conflicting data have been reported about the role of stress and depressive symptoms on endothelial function. Chen *et al*[46] reported adverse effects of negative emotions on peripheral endothelial function, while Olive observed no relationship between ED and self-reported stress or depressive symptoms[47].

AIM OF THE REVIEW

The aim of this narrative review was to provide an overview of the most important papers regarding ED detection through EndoPAT 2000.

A comprehensive search of English language articles was performed in the MEDLINE database without using other search filters except the publication interval between 2005 and 2020. Before 2005 no papers regarding EndoPAT 2000 in pediatric endocrinological and metabolic diseases have been found.

Four authors performed the search, the key words were endothelial dysfunction, Reactive Hyperemia Index, RHI, Peripheral Artery Tonometry, Endo-PAT 2000. For each challenging topic (T1DM, MS and cancer survivors) specific key words were associated and matched with the following terms: Type 1 diabetes mellitus, type 2 diabetes mellitus, obesity, metabolic syndrome, endocrine dysfunction, pituitary, cancer, growth hormone, glucocorticoids, thyroid hormones, estrogens, testosterone, neoplasm, malignancy.

A manual search in the reference lists of most significant papers was also performed. Studies conducted on patients aged more than 18 years or not written in English were excluded. Each study was screened by title and abstract.

For each eligible study we extracted the following data: author, year of publication, design of the study, population studied, control group (if available), RHI results, RHI outcomes. Results are summarized in Tables 1-3.

Table 1 Study characteristics for reactive hyperemic index-Endopat 2000 in different pediatric type 1 diabetes mellitus populations

Ref.	Study design	Aim of study	Population: age mean \pm SD or median (range); n [F/M]	Control group: age mean \pm SD or median (range); n [F/M]	RHI result: mean \pm SD or median (range)	Outcomes
Mahmud <i>et al</i> [51], 2006	RA	Determinate whether a gender contrast in a preclinical stage of atherosclerosis, or endothelial dysfunction, is present in pediatric diabetic patients.	T1DM Children for at least 1 yr, no microalbuminuria or retinopathy: 14.2 \pm 1.3, n = 20 [8/12]	Healthy children without a family history of hypercholesterolemia: 14.1 \pm 1.5, n = 20 [8/12]	1.85 \pm 0.45 <i>vs</i> 1.95 \pm 0.32 (diabetic <i>vs</i> controls) ^f . 1.61 \pm 0.32 <i>vs</i> 1.93 \pm 0.28 (male diabetic <i>vs</i> male controls) ^b . 2.21 \pm 0.35 <i>vs</i> 1.99 \pm 0.38 (female diabetic <i>vs</i> female controls) ^c . 1.93 \pm 0.28 <i>vs</i> 1.99 \pm 0.38 (male <i>vs</i> female control groups) ^c . 1.61 \pm 0.32 <i>vs</i> 2.21 \pm 0.35 (male <i>vs</i> female diabetic groups) ^b .	T1DM adolescents males worse RHI compared with similarly aged T1DM females and healthy gender and age matched controls. T1DM females had higher BMI and were more sexually mature.
Haller <i>et al</i> [48], 2007	RA	Assess the ability of RHI to serve as a surrogate marker of endothelial dysfunction in children with T1DM.	T1DM Children with disease > 1 yr: 14.4 \pm 1.5, n = 44 [22/22]	Healthy children, non-smokers and without a family history of medical premature CVD or hyperlipidemia: 14.1 \pm 1.5, n = 20 [8/12]	1.63 \pm 0.5 <i>vs</i> 1.95 \pm 0.3 (diabetic <i>vs</i> controls) ^a .	RHI lower in diabetic population. In this study children with T1DM had significantly higher mean systolic BP, mean total cholesterol and mean HDL compared to controls. No significant differences in age, BMI, diastolic BP, LDL or triglycerides were observed between the 2 groups.
Mahmud <i>et al</i> [49], 2008	RA	Evaluate the effect of a high-fat meal on RHI in adolescents with T1DM.	T1DM Children with disease > 2 yr, no retinopathy or nephropathy: 14.6 \pm 1.75, n = 23 [9/14]	Healthy children: 14.7 \pm 1.95, n = 23 [9/14]	Pre-meal RHI, T1DM <i>vs</i> controls, 1.78 \pm 0.4 <i>vs</i> 2.06 \pm 0.4 ^a . Post-meal RHI, T1DM <i>vs</i> controls, 1.45 \pm 0.3 <i>vs</i> 1.71 \pm 0.3 ^a .	RHI lower in diabetic population in a fasting state and after a high-fat meal compared with controls. The change in RHI was similar in the 2 groups.
Palombo <i>et al</i> [54], 2011	RA	To compare large artery structure and function indexes, endothelial function and regenerating capacity between T1DM adolescent and healthy age-matched controls. Association of different vascular measures with EPCs, glyco-metabolic control and AGEs, sRAGE and adiponectin levels were searched.	T1DM patients without retinopathy, microalbuminuria and neuropathy, pharmacological treatment (other than insulin). 18 \pm 2, n = 16 [5/11]	Healthy children: 19 \pm 2, n = 26 [11/15]	2.0 \pm 0.5 <i>vs</i> 1.8 \pm 0.6 (T1D <i>vs</i> controls) ^c . 1.5 \pm 0.4 <i>vs</i> 2.2 \pm 0.8 (T1D with HbA1c \geq 7.5% <i>vs</i> T1d with HbA1c < 7.5%) ^a .	T1DM adolescents higher central pulse pressure (PP), Augmentation Index (AI), carotid femoral pulse wave velocity, local carotid wave speed, common carotid artery intima-media thickness. RHI reduced only in T1DM patients with \geq 7.5% ($P < 0.05$). In the overall population, EPCs were an independent determinant of carotid IMT (together with adiponectin), while fasting plasma glucose was an independent determinant of carotid wave speed, AI and central PP.
Pareyn <i>et al</i> [50], 2013	CSS	To search a difference in RHI between w T1DM adolescents and controls	T1DM children insulin treated for at least one year: 15.8 (14.4 to 16.6), n = 34 [18/16]	Healthy children: 15.5 (13.9 to 16.2, n = 25 [13/12]	1.6 (1.3-2.0) <i>vs</i> 1.9 (1.7-2.4), children with T1DM <i>vs</i> controls ^a . 1.3 (1.3-1.7) <i>vs</i> 2.0 (1.7-2.5), female with T1DM <i>vs</i> female controls ^a . 1.8 (1.5-2.1) <i>vs</i> 1.8 (1.5-2.3), male with T1DM <i>vs</i> male controls ^c .	RHI lower in T1DM, especially in females. No correlation was seen between RHI and BMI SDS, BP SDS, HbA1c, age, disease duration, TG and Tanner stage.
Scaramuzza <i>et al</i> [52], 2015	CS	To evaluate prevalence of early EF, measured by RHI < 1.67 in T1DM cohort, at baseline and after a 1 yr follow-up	T1DM adolescents with disease duration > 1 yr, Tanner pubertal stage III-V, BMI between 5-95 ^o percentile: 16.2 \pm 3.5, n	No controls	1.26 \pm 0.22 <i>vs</i> 2.24 \pm 0.48, patients with RHI < 1.67 <i>vs</i> patients with RHI > 1.67 ^b . At the 1 yr follow-up in 64/73 patients, the rate of	RHI negatively correlates with impaired metabolic control and subclinical signs of autonomic neuropathy, while positively correlates with

			= 73 [25/48]		endothelial dysfunction (81.8%) was even higher than the rate recorded at baseline (76.7%).	regular physical activity. ED progression irrespective of improved metabolic control.
Scaramuzza <i>et al</i> [57], 2015	RA	To evaluate the effect of alpha-lipoic acid on ED in T1DM youth, a 6-month, double-blind, randomized controlled trial	T1DM adolescents for at least 1 yr, aged 12-19 yr, insulin requirement 0.5 U/kg/day, blood glucose checks more the 3 times/day, BMI and BP < 95 ^o percentile, no cardiovascular or inflammatory diseases. 16.3 ± 3.4, <i>n</i> = 71 [29/42], age at baseline.		3 double-blind study arms: 10000 ORAC antioxidant diet + (- lipoic acid, 1.40 ± 0.68 <i>vs</i> 1.72 ± 0.66 ^a (baseline <i>vs</i> after 6 months). 10 000 ORAC antioxidant diet + placebo, 1.39 ± 0.41 <i>vs</i> 1.58 ± 0.40 ^c (baseline <i>vs</i> after 6 months). Controls, 1.58 ± 0.64 <i>vs</i> 1.54 ± 0.42 ^c .	Positive association between alpha-lipoic acid administration and ED parameters.
Deda <i>et al</i> [53], 2018	RA	To evaluate the effect of Vit. D supplementation on EF by RHI measurement	T1DM patients for at least 2 yr and levels of 25-OH-Vit. D < 37.5 nmol/L. 15.7 ± 1.4, <i>n</i> = 31 [19/12]	To account for seasonality of RHI testing, a separate cohort of age, sex and T1DM matched controls was tested in spring and in fall (no significant difference was showed)	After a 4.8 ± 1.3 months Vit. D supplementation RHI improved: 1.83 ± 0.42 <i>vs</i> 2.02 ± 0.68 ^a .	Vit.D supplementation associated with EF improvement and reduced expression of urinary inflammatory markers.

^a*P*<0.05.^b*P*<0.005.^c*P*>0.05.

AGEs: Serum levels of advanced glycation end products; CS: Cohort study; CSS: Cross sectional study; CVD: Cardiovascular disease; BMI: Body mass index; BP: Blood pressure; ED: Endothelial dysfunction; EF: Endothelial function; EPCs: Endothelial progenitor cells; F: Female; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; M: Male; ORAC: Oxygen radical absorbance capacity units; RA: Research article; RHI: Reactive hyperemia index; SDS: Standard deviation score; sRAGE: Soluble receptors for AGEs; T1DM: Type 1 diabetes mellitus; TG: Triglycerides.

STUDY IN PEDIATRIC PATIENTS WITH DIABETES MELLITUS

We considered 6 studies on EndoPAT use in pediatric patients with T1DM aimed to evaluate precocious ED and 2 other studies aimed to evaluate a diet or drug effect in ED. Five of 8 studies compared RHI between T1DM patients and healthy children. In 3/5 studies RHI was significantly lower in patient group[48-50]; in particular, Pareyn *et al*[50] reported a significantly lower RHI, especially in T1DM females.

Males had a lower BMI and were less sexually mature (3 males were prepubertal, while all the females were post-pubertal)[51]. This might explain the difference reported since it has been described that prepubertal RHI is lower than in a mid-or late pubertal state[44,45]. No other differences between males and females have been reported[51].

T1DM patients evaluated by Haller *et al*[48] had a significantly higher values of systolic blood pressure, total and HDL cholesterol. Blood pressure levels did not always influence RHI in the majority of the studies[51-54], and similar results were found as regards lipid profile[49,51,52-54].

In 1/5 RHI was significantly lower in T1DM males than in females[51].

In the Pareyn cohort 5 patients were overweight or obese, but even after their exclusion RHI was significantly lower in T1DM subjects[50].

In 1/5 RHI was similar between T1DM and control group, although patients had higher central pulse pressure, augmentation index, carotid femoral pulse wave velocity, local carotid wave speed and common carotid artery intima-media thickness [54]. In this study RHI was significantly lower in patients with HbA1c ≥ 7.5% and decreased with diabetes duration.

Excluding the exceptions mentioned above, no differences in age, blood pressure and lipid levels were reported between T1DM and controls. As expected, HbA1c and fasting glucose levels were higher in patients. BMI was not significantly different in most studies[48,49,51], while in some it was not considered[50,54].

In 1/5 studies only T1DM adolescents were included[52]. They were considered to have ED if their RHI was < 1.67 and without ED if their RHI was > 1.67. RHI was significantly lower in 76.7% of patients, and after a one year follow-up increased to 81.8%. The authors reported that RHI was significantly correlated to HbA1c levels (both at baseline, and measured during the follow-up period), to subclinical signs of

Table 2 EndoPat 2000 in pediatric population with metabolic syndrome

Ref.	Design	Aim of the study	Population: age in years; mean \pm SD or median (range)	Control group: age in years; mean \pm SD or median (range)	RHI reported in arbitrary units. If RHI not specified, we reported p trend or positive/negative relation with parameters examined	RHI outcomes
Dongui <i>et al</i> [58], 2019	QRS	Impact of diet and exercise on microvascular function	Sedentary OB Age 12-18, $n = 57$ [F/M = 0/57]	Healthy NW Age 12-20, $n = 10$ [F/M 0/10]	OB 1.43 (0.35) <i>vs</i> CG 1.67 (0.36) ^a . After exercise OB <i>vs</i> CG ^a . OB Pre-exercise <i>vs</i> Post-Exercise ^a .	RHI higher in CG. In OB RHI improved after 6 wk of diet and exercise.
Pareyn A <i>et al</i> [59], 2015	CSS	Assessment of EF in OB/OW adolescents	OW/OB Age 14.7, $n = 27$ [F/M 11/16]	NW Age 15.5, $n = 25$ [F/M 13/12]	NW 1.88 (1.7-2.4) <i>vs</i> OW 1.5 (1.3-1.9) ^a . Positively with age ^a and tanner stage ^a . Negatively with diastolic BP ^a . With BGL, insulin lipid profile ^c .	RHI lower in OB/OW adolescents. RHI improved with age and Tanner stage. RHI decreased with higher diastolic BP. RHI not related with lipid, IR, BGL and gender. RHI inversely related with baseline pulse amplitude.
Agarwal <i>et al</i> [60], 2013	CSS	Assessment of EF in OB/NW adolescents	OB Age 15.3 (0.4) years, $n = 37$ [F/M 26/11]	NW Age 14.9 (0.6), $n = 14$ [F/M 9/5]	OB 1.7 (0) <i>vs</i> NW 1.9 (0.1) ^a . OB IGR 1.63 ^a . Other values reported like p trend.	RHI lower in obese adolescents. RHI negatively related with BMI, WC, BGL, HOMA-IR, Leptin, TNF, hs-CRP. No relationship with lipid profile and BP.
Mahmud <i>et al</i> [61], 2009	RA	Evaluation of EF in OB adolescents with impaired IS	OB with HOMA-IR 5.4 Age 13.4 (1.7), $n = 26$ [F/M 10/16]	NW, healthy Age 14 (1.4), $n = 51$ [F/M 21/30]	OB 1.5 (0.4) <i>vs</i> NW 2 (0.4) ^b . Other values reported like p trend.	EF lower in OB and negatively related with adiposity, TG, LDL and Tot-Chol. RHI improved with age. RHI not correlated with Leptin, IR or gender.
Tomsa <i>et al</i> [62], 2016	CSS	Comparing EF to body fat, IS, BGL and CIM in dysglycemic and OW adolescents	OW with NGT, $n = 25$, OW with IGT $n = 19$, OW with T2D but HB1Ac < 8% $n = 16$; Age 15.5 (0.2) Total $n = 60$ [F/M 37/23]	NW Age 15.5 (0.2), $n = 21$ [F/M 9/12]	BMI 30.91.2 (0) <i>vs</i> BMI 30.41.5 (0) <i>vs</i> BMI 26.72.0 (0) p trend ^a . Negatively with WC, BGL, TNF, PAI ^a , leptin ^b . Positively with age and insulin sensitivity ^a . BP, lipid profile ^c . For exact values see reference.	RHI lower in OB and T2DM. RHI negatively related with percentage body fat, WC, Leptin, TNF-alpha, BGL. RHI positively related with age and. RHI not related with BP and lipid profile.
Del Ry <i>et al</i> [63], 2016	RA	C-type Natriuretic Peptide in OW, OB and NW. Relation with RHI and other endothelial markers	OW AGE 12.8 (1.6) $n = 10$; [F/M 5/5]. OB, G 3.5 (1), AGE 12.8 (1.6) $n = 45$; [F/M19/26].	NW, AGE 12.8 (1.4) $n = 27$; [F/M 14/13]	NW 2.1 (0.2) <i>vs</i> OW 1.6 (0.4) ^a . NW <i>vs</i> OB 1.4 (0.3) ^b . Negatively with CNP ^b . Exact values non reported.	RHI was significantly lower in OW/OB. CNP negatively related with RHI.
Del Ry <i>et al</i> [64], 2020	RA	Natriuretic peptide network in normal weight and obese adolescents, its relation with RHI.	Primary OB Not diabetic, Age 13.3 (0.5) $n = 16$; [F/M8/8].	NW, Age 14.3 (0.4) $n = 24$; [F/M14/10].	NW 2.1 (0) <i>vs</i> OB 1.4 (0) ^b . Negatively with CNP, hs CRP, diastolic BP ^b . Exact values non reported.	RHI significantly lower in OB. RHI negatively related with hs-CRP, CNP, diastolic BP, fat mass and A1C.
Singh <i>et al</i> [65], 2017	RA	Relation between EF and urinary markers	OW and OB Age 13.8 (2.4) $n = 43$; [F/M 23/20]	Healthy NW Age 13.9 (2) $n = 20$; [F/M 8/12]	NW 1.6 (0.1) <i>vs</i> OW 1.66 (0.1) ^c and OB 1.67 (0.1) ^c . NW girls 1.9 <i>vs</i> NW boys 1.25 ^b .	No correlation between RHI, BMI and urinary markers. RHI higher in NW female adolescents
Czippelova <i>et al</i> [66], 2019	RA	Assessment of EF in different systemic vascular resistances. Comparing EF to Cardio Ankle Vascular Index	OB No DM or HBP Age 16.4 (2.7) $n = 29$ [F/M 14/15]	NW Age 16.5 (2.6) $n = 29$ [F/M NR]	NW 1.45 (0.3) <i>vs</i> OB 1.4 (0.3) ^c . Positively with SVR ^a .	No difference between RHI in OB and CG RHI was influenced by vascular tone and resistance. RHI in OB positively related with SVR.
Kochummen <i>et al</i> [24], 2019	CSS	Evaluation of EF in OB with normal BGL comparing to NW with T1DM1 and OB with T2DM	NW with DM1 and OB DM2 Age 12.7 (3.8) $n = 41$ [F/M 25/16]	OB with normal BGL, BP and lipid profile. Age 12.8 (2.7) $n = 17$ [F/M 9/8]	A1C > 10% 1.2 (0.2) <i>vs</i> A1C < 10% 1.7 (0.6) ^a . Negatively with A1C ^a . DM 1.4 (0.5) <i>vs</i> obese 1.4 (0.3) ^c . T1D 1.4 (0.5) <i>vs</i> T2D 1.5 (0.5) ^c . Female 1.5 (0.5) <i>vs</i> male 1.3 (0.4) ^a .	RHI lower in poorly controlled DM. RHI negatively related with A1C. RHI similar between OB and NW with DM and between DM1 and DM2. RHI lower in males especially in OB without

						DM.
Bruyndonckx <i>et al</i> [67], 2014	CSS	Evaluation of EF and correlation with CVRF in children	OB Age 15.2 (1.4) <i>n</i> = 57	NW Age 15.5 (1.5) <i>n</i> = 30	NW 2 (0.6) <i>vs</i> OB 2.2 (0.7) ^c . Lipid, HOMA-IR, BP, hsCRP ^c .	RHI not related with BMI, HOMA-IR, BP, lipid or hsCRP. RHI not homogenous with "Time to peak".
Tryggestad <i>et al</i> [68], 2012	RA	Evaluation of vascular function in OB and NW children	OB Age 13.9 (2.5) <i>n</i> = 62 (F/M 32/30)	NW Age 13.3 (3) <i>n</i> = 61 (F/M 30/31)	OB <i>vs</i> CG ^c . Exact values reported for age and BMI (see reference). Age group 8-12 yr: 1.6-2.0 ^a . Age group 13-18 yr: 2.0-2.5 ^a .	RHI similar in OB and CG. RHI improved 0.07 for each year of age in CG. RHI was reduced in older OB. RHI not related with BP and lipid profile.
Fusco <i>et al</i> [69], 2020	RA	Assessment of precocious microvascular dysfunction in OB adolescents	OB Age 14.1 (2.5), <i>n</i> = 22 [F/M 13/9]	NW Age 15.1 (1.5) <i>n</i> = 24 [F/M 11/13]	OB 1.8 (0.6) <i>vs</i> CG1.9 (0.5) ^c .	RHI not different between CG and OB. RHI not correlated with LDF (that is impaired in OB).
Bacha <i>et al</i> [74], 2017	CSS	Comparing EF in hispanic adolescents with and without NAFLD	OW with pre diabetes or T2DM with NAFLD Age 15.2 (0.5) <i>n</i> = 23 [F/M 12/11]	OW with pre-diabetes or TD2 without NAFLD Age 15.7 (0.4) <i>n</i> = 13 [F/M 3/10]	NAFLD 1.4 (0) <i>vs</i> CG 1.7 (0) ^b .	Hepatic fat and AST/ALT levels were inversely related with RHI.

^a*p* < 0.05.^b*p* < 0.005.^c*p* > 0.05.

A1C: Glycosylated hemoglobin; AE: Anti-epileptic drugs; CIM: Circulating inflammatory markers; CNP: C-type natriuretic peptide; CSS: Cross sectional study; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; CVR: Cardio vascular risk; CVRF: Cardio vascular risk factors; EF: Endothelial function; HBP: High blood pressure; IGT: Impaired glucose tolerance; IR: Insulin resistance; IS: Insulin sensitivity; LDF: Laser Doppler flowmetry; NW: Normal weight; OB: Obese > 95th cc; OS: Oral steroids; OW: overweight > 85th cc; NGT: Normal Glucose Tolerance; PM: Psychiatric medications; QRS: Quasi randomized study; RA: Research Article; SVR: Systemic vascular resistance; TG: Triglycerides; Tot-Chol: Total cholesterol; RHI: Reactive hyperemic index; WC: Waist circumference.

autonomic neuropathy and to physical activity[52]. However, RHI did not correlate to gender, carotid intima media thickness, insulin requirement, dietary habits and body composition[52].

Inter-individual values of RHI in some studies were not correlated to Hb1Ac[48,50,51] age and disease duration[50-52], BMI or lipid profile[48,50-52,54], blood pressure [48,51,52], fasting glucose levels[48-54], or pubertal stage[51]. Pareyn *et al*[50] described a weak correlation between inter-individual RHI and Low Density Lipoprotein (LDL), however this correlation was counterintuitive and might be a type I error.

An interesting study by Heier *et al*[55] was not included in Table 1, since mean age was 20.8 ± 1.8 years. ARHI < 1.67 was reported in 30.4% of patients with diabetes and in 21.4% of controls. This might indicate that the cut-off reported by the Mayo study was not ideal for assessing cardio vascular disease (CVD).

A double blind, randomized, placebo-controlled trial (RCT) was conducted in 443 T1DM adolescents at high-risk of CVD and renal complications, defined as albumin-creatinine ratio (ACR) in the upper tertile of range[56]. The aim of this study was to evaluate the effect of ACE inhibitor, statin and combinations of both interventions or placebo. In addition a parallel observation cohort of T1DM subjects defined as low-risk of complications (ACR in lower and middle tertiles) was compared with the untreated group. To evaluate ED, RHI in 158 patients from the RCT and 215 patients from the observation cohort was evaluated[56]. No differences in RHI were observed between high- and low-risk CVD participants in the observational study[56]. Neither ACE nor statin use had any effect on RHI in RCT. During the follow-up RHI increased. An improvement of microvascular function possibly due to stature and pubertal development might explain this result[44,56]. The authors reported that adjusting RHI for body mass normalized RHI to baseline values[56].

1/8 studies investigated the effect of Vit. D supplementation in ED in T1DM patients with 25-OH-VitD levels < 37.5 nmol/L[53]. An improvement of RHI after 4.8 ± 1.3 mo follow-up has been reported.

1/8 studies used EndoPAT to evaluate the effect of an alpha-lipoic acid and antioxidant diet in adolescents with T1DM in a double blind trial, and an improvement in the group treated with 10000 ORAC antioxidant diet +lipoic acid has been reported[57].

Table 3 Study characteristics for reactive hyperemic index-Endopat 2000 in different pediatric endocrine populations

Ref.	Study design	Aim of study	Population: age mean \pm SD or median (range); n [F/M]	Control group: age mean \pm SD or median (range); n [F/M]	RHI result: mean (SD)	Outcomes
Bhangoo <i>et al</i> [44], 2011	CSS	Relation of puberty and sex steroids with endothelial function	Healthy population: Tanner I: 12.1 (0.6), n = 21 [19/2] Tanner II-III: 12.7 (0.7), n = 35 [21/14] Tanner IV-V: 13 (0.7), n = 33 [22/11]		Tanner I 1.46 (0.44) <i>vs</i> Tanner II-III 1.71 (0.35) ^a . Tanner I 1.46 (0.44) <i>vs</i> IV-V 1.92 (0.38) ^b . Tanner II-III value n.avs IV-V value NA ^a . F Tanner II-III 1.66 (0.38) <i>vs</i> F IV-V 1.91 (0.29) ^a . M Tanner I 1.41 (0.35) <i>vs</i> M Tanner II-III 1.78 (0.30) ^b . M Tanner I <i>vs</i> M Tanner IV-V 1.93 (0.67) ^a .	PAT index positively related with estradiol, DHEAS levels and age.
O'Gorman <i>et al</i> [94], 2012	CCS	Evaluation of EF in TS, and HC.	Turner syndrome: 13.5 (2.4), n = 15 [15/0]. Turner syndrome: GH-untreated 14.3 (2.4), n = 8. Turner syndrome: GH-treated 12.7 (2), n = 7.	Healthy children (HC) 14.3 (1.7), n = 15 [15/0]	Turner syndrome: 1.64 (0.34) <i>vs</i> HC 2.08 (0.32) ^b . Turner syndrome: GH-untreated 1.44 (0.26) <i>vs</i> GH-treated 1.86 (0.28) ^a .	PAT index lower in TS indicating impaired EF compared with HC.GH may protect endothelial function in TS.
Ruble <i>et al</i> [78], 2015	CCS	Evaluation of RHI in ALL survivors, compared with HS.	ALL survivors: (0.9), n = 16 [8/8]. HS:13.8 (0.9), n = 16 [6/10].	HS: 14.3 (1.7), n = 15 [15/0]	ALL survivors 1.54 (0.38) <i>vs</i> HS 1.77 (0.41) ^a .	Poorer vascular health ALL survivors.
Blair <i>et al</i> [77], 2014	RCCT	Evaluation of flavanoid-rich purple grape juice (compared in RCCT with clear apple juice) on endothelial function, markers of oxidative stress and inflammation in cancer survivors.	Cancer survivors (hematopoietic malignancy 50%, solid tumor 50%) 16.4 (13.7–17.2), n = 24 [17/7]		Cancer survivors. Before apple juice 1.57 (0.36) <i>vs</i> before grape juice 1.75 (0.52). After apple juice 1.83 (0.47) <i>vs</i> after grape juice 1.75 (0.39). Before grape juice 1.57 (0.52) <i>vs</i> after grape juice 1.75 (0.39).	After four weeks of daily consumption of flavanoid-rich purple grape juice, no measurable change in vascular function in young cancer survivors.

^aP<0.05.^bP<0.005.

CSS: Cross sectional study; CCS: Case control study; F: Female; GH: Growth hormone; HC: Healthy controls; HS: Healthy siblings; ALL: Acute lymphoid leukemia; M: Male; NA: Not available; RHI: Reactive hyperemic index; RCCT: Randomized controlled crossover trial.

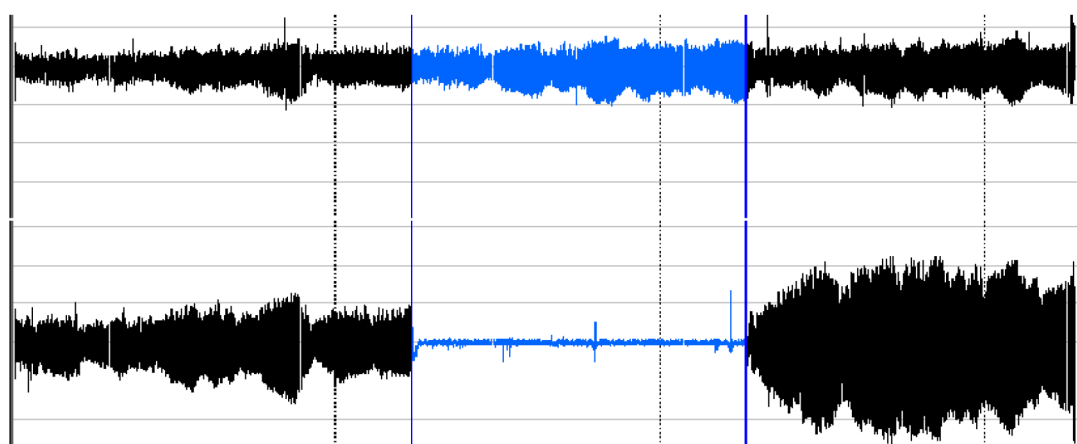


Figure 1 Patient with type 1 diabetes mellitus, the upper highlighted line shows normal flow in the non-occluded right arm. The lower highlighted line shows total occlusion in the left occluded arm. The picture shows a non pathologic post-occlusion dilation with RHI 1.8, despite this value is lower than mean values for young healthy boys.

Most of the studies reported an ED in young adults with diabetes mellitus as compared with healthy controls despite an absence of clinical manifestation of CVD, other co-morbidities (*e.g.*, retinopathy or microalbuminuria) or traditional cardiovascular risk. RHI correlation with glycemic control is unclear; in some studies RHI was negatively related with HbA1c or diabetes duration. The evaluation with

EndoPAT in pediatric age is likely difficult due to the physiological development through puberty. Maybe EndoPAT might be helpful in evaluating the effect of some external interventions (*e.g.*, medication or diet).

STUDY IN PATIENTS WITH METABOLIC SYNDROME

We considered 14 studies describing the use of EndoPAT 2000 for the assessment of ED in adolescents with MS, reporting conflicting results. The following parameters were considered: BMI, T1DM and T2DM, gender, pubertal stage, age, polycystic ovary syndrome (PCOS), blood pressure (BP) values, non alcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA), lipid profile, IR and insulin sensitivity (IS) indexes, plasma glucose (PG) levels, inflammatory markers (Urinary Markers, CNP, PAI, Adiponectin, Resistin, micro RNA-126, VCAM-1, E-Selectin, I-CAM, saturated fatty acids). Results of the most important studies are reported in Table 2.

As regards BMI, in 7/14 studies RHI was significantly lower in obese adolescents [58-64]. In particular, Donghui *et al* [58] evaluated obese males and showed improvement of RHI after six weeks of diet and intensive training. They concluded that EndoPAT 2000 is a useful tool to evaluate vascular endothelial function [58]. In Mahmud *et al* [61] RHI was negatively related with BMI and lipid profile, but not with IR indexes and adipocytokine levels. In Tomsa *et al* [62] waist circumference was the main determinant of ED ($P = 0.0004$). However, in 6/14 studies RHI did not correlate with BMI [24,65-69]. In the study of Czipelova *et al* [66] RHI was not influenced by BMI, but was related with systemic vascular resistance. In Bruyndonckx *et al* [67] RHI was similar in obese and controls, while time to peak was significantly lower in obese. Similar results were reported by Hudgins *et al* [70]. In Fusco *et al* [69] RHI was similar in obese and controls. They also evaluated laser Doppler flowmetry (LDF) as a marker of precocious microvascular damage, and showed LDF lower levels in obese as compared to controls. They concluded that precocious ED in childhood obesity cannot be evaluated by RHI [69].

To our knowledge, 2/14 studies compared RHI to T1DM and T2DM [62,67]. In particular in Kochummen *et al* [24] mean RHI in obese adolescents without diabetes was similar to T1DM and T2DM patients. RHI was lower if compared with healthy controls obtained by other authors, and decreased of 0.09 for each 1% increase of HbA1c, but no difference was observed between patients with T1DM and T2DM. In Tomsa *et al* [62] RHI was higher if HbA1c was less than 5.5%, and was lower in T2DM obese.

In 2/14 studies RHI was higher in female adolescents. In particular RHI was higher only in girls belonging to the control group [24,65]. Conversely, RHI was not different between boys and girls [61]. RHI was positively related with Tanner Stage in one study [59], while another study did not report difference between pre-pubertal and pubertal children [24].

In 4/14 studies RHI improved with age [59,61,62,68]. In Tryggestad *et al* [68] RHI improved of 0.07 units for each year of age in control group only, but not in obese subjects. In two studies RHI decreased with age in obese adolescents, especially older than 15 years, maintaining this trend in adulthood. It has been suggested that in obese subjects RHI is not precociously impaired, but more time is needed to establish endothelial damage. In 1/14 study RHI was similar among different age groups [24]. Another study in pediatric population showed RHI improvement following increasing height and stage [45].

Lowenstein *et al* [71] found that RHI was lower in women with PCOS. The study did not include pediatric patients, however, it is important since girls with MS are at risk of developing PCOS. Other authors showed that EF was similar before and after 3 mo of metformin treatment for PCOS, suggesting that longer periods of metformin are needed to evaluate its positive effect on endothelial function [72,73].

In 5/14 studies RHI was not related with blood pressure values [60-62,67,68], while in 2/14 studies RHI was inversely related with blood pressure, but only with the diastolic ones [59,64].

Only in the study of Bacha *et al* [74] RHI was not compared with BMI. In this study RHI was negatively related with NAFLD, liver enzyme levels and liver-fat deposition. Moreover, RHI was negatively associated with augmentation index, which was higher in patients with NAFLD [74]. Kheirandish-Gozalel *et al* [75] evaluated RHI twice a day (morning and evening) and showed that RHI was lower in morning than in evening, and related with OSA severity score. They concluded that RHI was significantly lower than in controls and confirmed the usefulness of EndoPAT

instrument. Only in 1/14 studies RHI was negatively related with total cholesterol ($P < 0.01$), triglycerides ($P < 0.04$), and LDL ($P = 0.02$) levels, but not with HDL levels[61]. In 5/14 studies RHI was not related with lipid profile[59,60,62,67,68]. On 1/14 studies RHI was negatively related with IR indexes[60] and in another study RHI was positively related with insulin sensitivity index[62]. In other 4/14 studies RHI was not statistically related with IR indexes[59,61,67,68].

In 2/14 studies RHI was not related with fasting PG[59,61] while in 4/14 studies RHI was negatively related with PG[24,60,62,64].

In 2/14 studies RHI was inversely related with Leptin and TNF-alpha levels[60,62], and in 3/14 studies RHI was inversely related with HSCRP[60,63,64]. As for other aspects of metabolic syndrome these results were not homogenous. In 3/14 studies RHI was not related with HSCRP[65,67,68], and in 2/14 studies RHI was not related with Leptin levels[61,65]. In some studies RHI was compared to other inflammatory markers less used to assess endothelial function[58,61-65,74,76]. None of these reported LnRHI. Only one study (not in table) reported "Peak response" instead of RHI[70].

Chen *et al*[76] studied RHI and its relationship with HOmeostatic Model Assessment of Insulin Resistance (HOMA-IR). RHI was evaluated in 257 healthy adolescents (138 F/119M) and was negatively related with HOMA-IR ($P = 0.001$), and not with gender, lipid profile, BP values[75].

In 3/14 studies limitations were not reported[58,70,65]. Mahmud *et al*[61] evaluated controls recruited from other studies, and IR and adipocytokine levels from control group are not known. Tomsa *et al*[62] evaluated patients with T2DM during metformin therapy which is recognized to influence endothelial function. In 5/14 studies patients' samples were small, including 41, 45, 37, 27 and 29 participants, respectively[24,59,60,64,66]. Bacha *et al*[74] evaluated Hispanic population, while Mahmud *et al*[61] enrolled Caucasian adolescents. In 1/14 study are reported limitations about the reliability of RH-PAT[59]. Pareyn *et al*[59] concluded that an unequivocal theory about the underlying mechanism is lacking. There is some uncertainty about the relative importance of endothelium dependent and independent vasodilatation factors in the RH-PAT response. Vascular bed and RH-PAT are highly responsive to sympathetic tone and to emotional responses like anger, depression, anxiety[59].

ENDOTHELIAL FUNCTION IN CANCER SURVIVORS

To our knowledge two studies analyzed ED by Reactive Hyperemia Index – Peripheral Artery Tonometry (RHI-PAT) in childhood cancer survivors (Table 3).

Blair *et al*[77] examined microvascular endothelial function in childhood cancer survivors off therapy for more than three years; 21 out of 24 participants received cardiovascular toxic chemotherapies (anthracyclines or platinum agents), and/or radiation. They showed low/borderline RHI-PAT value without measurable change in vascular function after four weeks of supplementing meals with flavonoid-rich purple grape juice.

Ruble *et al*[78] compared 16 acute lymphoblastic leukemia (ALL) survivors from one to ten years off therapy, with 16 healthy siblings matched by gender and age. All but one survivor has been treated with anthracyclines with a mean cumulative dose of 148 mg/m² and nearly one third has undergone cranial radiation. In this study, adolescent ALL survivors had significant lower RHI-PAT (Table 3), despite similar cardiovascular clinical risk factors with control group, including BMI, blood pressure values and waist to height ratio (marker of central adiposity), marker of fitness (assessed by Six Minute Walk Test). However, more survivors than siblings resulted overweight or obese (44% *vs* 31%). No data are available about lipid profiles, despite previous study on long-term survivors[79,80] have suggested that abnormal triglycerides levels contribute to macrovascular ED measured by endothelial dependent ultrasound flow-mediated dilation (% of change in brachial artery diameter after 5 min of occlusion).

Little is known about the incidence and predisposing factors of ED after radiotherapy. Dengel *et al*[79] found no difference in endothelial function in survivors who underwent cranial radiotherapy in addition to chemotherapy compared with control group of similar gender, age, and weight. In a subsequent cross-sectional study Zelcer *et al*[81] showed ED in 13 Hodgkin lymphoma young adult survivors who had received mediastinic radiotherapy compared with healthy gender- and age-matched controls, as evidenced by lower RHI-PAT (1.67 ± 0.39 *vs* 2.03 ± 0.37 , $P < 0.01$). No correlation between PAT scores in controls and Hodgkin lymphoma survivors was found for any of the classic cardiovascular risk factors (BMI, systolic and diastolic

blood pressure, serum LDL, HDL, and triglycerides levels). Vatanen *et al*[82] demonstrated that childhood cancer survivors treated with total body irradiation (TBI) develop indirect signs of endothelial damage during adulthood, including decreased arterial lumen size and an increased carotid intima-media thickness, but no pediatric studies have used RHI-PAT to detect endothelial function after TBI.

ENDOTHELIAL IMPAIRMENT IN PITUITARY DYSFUNCTION

Endothelial function testing has received growing interest as early marker of cardiovascular risk in pediatric endocrine diseases. During puberty, a complex interplay between metabolic and hormonal factors may affect endothelial function, the hypothalamus pituitary axis plays a central role in this complex network, although the exact mechanisms are not completely understood[42]. Estrogens can potentially enhance the endothelial-dependent flow mediated vasodilatation *via* the production of NO (nitric oxide) by endothelial NO synthase enzyme. In several *in vitro* animal models, it was shown that endothelial NO production and vasodilatation increases during puberty. In two different clinical studies, significant correlations with RHI-PAT were observed for pubertal stage[83,84].

Bhangoo *et al*[44] demonstrated that an increase in the RHI with pubertal advancement was related to an increase in sex hormones. In a healthy population of 89 children and adolescents, pubertal staging was based on ultrasensitive estrogen assays. A positive correlation between RHI-PAT and steroid hormone levels was found.

Radtke *et al*[45] confirmed this observation in two separate prospective cross-sectional studies. These included 112 healthy, normal weight and normotensive 10–16 year old children and adolescents, classified using a validated self-assessment tool, according to Tanner Stage, in 3 groups: prepubertal, (Tanner I); mid-puberty (Tanner II-III); late puberty (Tanner IV-V). Prepubertal children had a significantly lower RHI-PAT as compared to mid-puberty or late puberty groups (Table 3). In contrast to the results of Bhangoo *et al*[44], they found significant negative correlations between RHI-PAT and both stature ($r = 0.553$; $P < 0.001$) and BMI ($r = 0.309$; $P = 0.001$). Significant negative correlations were also observed between RHI-PAT and both age ($r = 0.567$; $P < 0.001$) and systolic blood pressure levels ($r = 0.494$; $P < 0.001$). However, in stepwise regression analysis pubertal status was the only independent predictor of ED ($R^2 = 0.242$; $\beta = 0.492$; $P < 0.001$). In both studies an important limitation lies in the methods used to determine the Tanner Stage, since pubertal stage was assessed by a self-administered questionnaire[85] or based on ultrasensitive serum estradiol levels, rather by physical examination.

The reduction of nitric acid (NO) also occurs in patients with growth hormone deficiency (GHD) due to reduction of local IGF-I, which causes dependent endothelial vasodilatation through the stimulation of NO production[86]. Moreover, GHD may contribute to the ED by increasing reactive oxygen species (ROS)[87].

On the other hand, there are studies showing an impairment of endothelial function in endocrine disease caused by hypersecretion of GH[88]. Although low level of IGF-1 is associated with ED, high IGF-1 is also related with increased endothelial impairment and cardiovascular disease[89,90]. In acromegaly, the mechanisms underlying this effect could be an imbalance between endothelium derived vasodilators (particularly NO) and ROS, together with increase of blood pressure, insulin and lipid profile values[91,92]. Along with these risk factors, GH and insulin-like growth factor-1 (IGF-1) can directly cause changes in macrovascular structures by vasoconstriction IGF-1 mediated *via* the nitric oxide synthesis or damage to vascular smooth muscle cells[93].

Despite several studies have analyzed the role of GH deficiency or hypersecretion in ED in adulthood, only one study has focused on pediatric age. In a cross-sectional case-control study, O’Gorman *et al*[94] found that adolescents with Turner syndrome (TS) had impaired endothelial function compared to healthy age-, gender- and BMI-matched controls. In TS GH therapy may protect endothelial function. Indeed, RHI-PAT scores were higher in girls receiving GH therapy than in those not receiving it (Table 3) and there was no significant difference in RHI-PAT scores between TS receiving GH therapy and control population (1.86 ± 0.28 vs 2.08 ± 0.32 , respectively, $P = 0.14$). In the same study, RHI-PAT scores in TS population did not vary with estrogen replacement therapy [1.56 ± 0.30 with estrogen replacement ($n = 6$) vs 1.69 ± 0.37 without estrogen replacement ($n = 9$), $P = 0.64$]. The study is limited by several factors: the small number of patients, the lack of data about pubertal status, independent cardiovascular risk factors in TS patients (including 1 patient with a history of

coarctation repair).

To our knowledge, no studies have investigated the possible relationships between ED and pituitary disorders in pediatric age.

CONCLUSION

Results from data on healthy populations suggest that a low RHI-PAT in children and adolescents is more likely to reflect juvenile microvascular response due to immature endothelial function rather than pathological dysfunction. Therefore, the risk thresholds established for the adult population cannot be used without necessary considerations in pediatric age. GH therapy may restore ED associated with growth hormone deficiency and may offer endothelial protection in girls with TS. IGF1 is considered as a key molecule in the pathogenesis of microvascular damage. There is a need of new studies to evaluate the endothelial function in other pediatric hypothalamus-pituitary axis disorders.

Oncological therapies may impair endothelial function and microvascular structure. Several chemotherapies and radiotherapy are risk factors for cardiovascular disorders in childhood cancer survivors. Therefore, it is essential to monitor microvascular endothelial function and long-term follow-up of survivors is recommended. Assessment of ED in cancer survivors, by a non-invasive and easily reproducible methodology as RHI-PAT, may have a role in the early identification of late effects in patients at high risk of cardiovascular events who could benefit from cardioprotective pharmacological interventions. However, there are no established reference values in children, and it is unknown the reliability of RHI-PAT to predicting adverse cardiovascular events. Therefore, due to lack of reference ranges, evaluation of PAT remains a research tool.

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