بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
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Effectiveness and feasibility of nail fold microcirculation test in screening for vascular complications in patients with type 1 diabetes mellitus

A thesis

For fulfillment of Master Degree in Pediatrics

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قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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List of Contents

List of abbreviations

ADA	American diabetes association
ADMA	Asymmetric dimethylarginine
AER	Albumin excretion rates
ANA	Antinuclear antibodies
ANGPT	Angiopoietin
ANGPTL4	Angiopoietin-like 4
AUC	Area under curve
CI	Confidence interval
CMV	Cytomegalovirus
CSII	Continuous subcutaneous insulin infusion
CTDs	Connective tissue diseases
CVD	Cardiovascular diseases
DCCT	The Diabetes Control and Complications Trial
DLP	The prevalence of dyslipidemia
DNA	Deoxyribonucleic acid
DNS	Diabetic Neuropathy Symptom Scor
DPN	Diabetic peripheral neuropathy
DR	Diabetic retinopathy
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarization
EDV	Exercising end-diastolic volume
EPCs	Endothelial progenitor cells
ESRD	End-stage renal disease
FBG	Fasting blood glucose
FMD	Foot-and-mouth disease
FPG	Fasting plasma glucose
GBM	Glomerular basement membrane
HbAlc	HemoglobinA1c

HIF	Hypoxia-induced factor
ICAM	Intercellular adhesion molecule
IL	Interleukin
IMT	Intimae media thickness
MNSI	Michigan Neuropathy Screening Instrument
MODY	Maturity-onset diabetes of the young
NO	Nitric oxide
NOS	Nitric oxide synthases
NPV	Negative predictive value
OGTT	Oral glucose tolerance test
PGI_2	Prostaglandin inhibitor 2
PPV	Positive predictive value
ROC	Receiver operating characteristic curve
ROS	Reactive oxygen species
RP	Raynaud's phenomenon
SSc	Systemic sclerosis
T1D	Type 1 diabetic
T1DM	Type1 diabetes mellitus
TCSS	Toronto Clinical Scoring System
TEDDY	Environmental Determinants of Diabetes in the Young
TNF	Tumor necrosis factor
TNFR	TNF receptor
TP	Thromboxane prostanoid
UV	Ultraviolet
VPT	The vibration perception threshold
VSMC	Vascular smooth muscle cells
vWF	Von Willebrand factor

List of Tables

List of Figures

ABSTRACT

Background: Advanced glycation-end products, low grade inflammation, and microangiopathy are implicated in the pathogenesis of diabetic vascular complications. Nail-fold videocapillaroscopy (NVC) is an easy and non-invasive tool of microvasculature assessment. Scarce reports addressed the utility of NVC in early detection of vascular complications among people with Type-1 diabetes-mellitus (T1DM).

Aims: to compare the NVC changes in adolescents with T1DM to healthy controls, and to correlate them to diabetes-duration, glycemic-control and various diabetic vascular complications.

Methods This case control study included Hundred thirty-five adolescents with T1DM. They were compared to 135 age and sex matched healthy controls. History included diabetes duration, insulin-therapy and symptoms of diabetic complications. Fundus-examination and Toronto-clinical scoring system (TCSS) were done. Fasting lipids, fraction-C of glycosylated hemoglobin (HbA1C %) and Urinary albumin-excretion (UAE) were measured. Nerve conduction velocity was done and NVC was performed using a ZL102-NVC.

Results

Eighty adolescents with T1DM (56.3%) had G4 NVC, 40 had G3 (31.9%), thirteen had G2 (10.4%) and 2 had G1 (1.5%). T1DM adolescents had more significant NVC changes than controls ($P < 0.001$). In addition T1DM adolescents with diabetic neuropathy, retinopathy, and nephropathy had significantly higher NVC changes than those without these complications ($P=0.003$, $P<0.001$ and $P<0.001$, respectively). Significant positive relation was found between NVC changes and diabetes duration ($P=0.001$), HbA1C (0.004), diabetic-neuropathy (0.003) and LDL (0.007). Upon performing multivariate logistic-regression for predictors of T1DM microvascular complications, insulin dose ($P=0.001$), NVC ($P=0.007$) and TCSS ($P=0.005$) were the most important predictors of neuropathy, while, insulin dose ($P=0.004$) and NVC ($P<0.001$) were the most important predictors of nephropathy.

Conclusion

Adolescents with T1DM having nephropathy, neuropathy and retinopathy have significantly higher NVC changes than those without complications and controls. Thus, NVC can be a useful and noninvasive tool for early assessment of the risk of vascular complications among adolescents with T1DM.

Introduction

Type1 diabetes mellitus (T1DM) is an autoimmune disease characterized by immune mediated B cell destruction and consequent insulin deficiency. This leads to metabolic disorders with chronic hyperglycemia as the main feature, which in turn causes exceeded production of advanced glycolysation end products leading to macrophage activation, increased oxidative stress and production of inflammatory cytokines **(Rogal et al., 2019)**.

Chronic inflammation causes endothelial dysfunction which in turn is the key event in the development of diabetic microvascular and macrovascular complications **(Paul et al., 2020)**. Endothelial dysfunction plays a crucial role in the development of T1DM vascular complications. Chronic hyperglycemia leads to decreased bioavailability of nitric oxide, increased oxidative stress, disturbances in intracellular signal transduction, and activation of advanced glycation end products, which results in endothelial dysfunction **(Bakirci et al., 2019)**.

This endothelial dysfunction causes increased production of inflammatory cytokines and augmented expression of cellular adhesion molecules resulting in a pro-inflammatory and prothrombotic state, eventually leading to microangiopathy. These changes are observed in the early stages of disease pathogenesis before the occurrence of overt macro and microvascular complications (**Kaur et al., 2018)**.

Several methods were invented to assess the microvascular damage in T1DM including doppler flow-metry, direct and indirect ophthalmoscopy, and ambulatory blood pressure monitoring **(Hosking et al., 2014)**.

Nailfold capillaroscopy is commonly used to investigate skin microcirculation. It is an easy, noninvasive, simple, fast, and economical, and effectively identifies peripheral microvascular **(Ruaro et al., 2020).** Nail fold videocapillaroscopy (NVC) evaluates structural changes of capillaries such as tortuosity, elongation, extension, and cross-linkage **(Souza & Kayser, 2015 and Ribeiro et al., 2012).** The role of NVC is increasing in the evaluation of patients with connective tissue disease. In the last decade, some studies evaluated the importance of NVC in non-rheumatic diseases such as T1DM **(Romano et al., 2015)**. However, no studies addressed its utility in pediatrics and adolescents with T1DM on a large scale and it's relation to diabetic micro and macrovascular complications

Aim of the Work

To evaluate the effectiveness and feasibility of nail fold microcirculation assessment in early detection and prediction of diabetic vascular complications. Moreover, to correlate these microvascular changes to the duration of DM, glycemic control and diabetic vascular complications (diabetic retinopathy, nephropathy, neuropathy and hyperlipidemia).

Type 1 Diabetes Mellitus

T1DM is a chronic illness characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. Most pediatric patients with diabetes have type 1 and a lifetime dependence on exogenous insulin (**Katsarou et al., 2017)**.

Most cases (95%) of T1DM are the result of environmental factors interacting with a genetically susceptible person (**Saberzadeh et al., 2018).**

This interaction leads to the development of autoimmune disease directed at the insulin-producing cells of the pancreatic islets of Langerhans. These cells are progressively destroyed, with insulin deficiency usually developing after the destruction of 90% of islet cells (**Burrack et al., 2017).**

Clear evidence suggests a genetic component in T1DM. Monozygotic twins have a 60% lifetime concordance for developing T1DM, although only 30% do so within 10 years after the first twin is diagnosed. In contrast, dizygotic twins have only an 8% risk of occurence, which is similar to the risk among other siblings. The frequency of diabetes development in children with a mother who has diabetes is 2-3%; this increases to 5-6% for children with a father who has T1DM (**Wang et al., 2017).**

Human leukocyte antigen (HLA) class II molecules DR3 and DR4 are associated strongly with T1DM. More