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Инасс Шалтоут[1], Мэри Уади[1], Мазен Аттиа[1], Ая Кхафаги[2], Сара А. Хассан[1]

[1] — Медицинский факультет Каирского университета, Каир, Египет
[2] — Студенческая больница Каирского университета, Каир, Египет

КОРРЕЛЯЦИЯ МЕЖДУ ПОРАЖЕНИЕМ МЕЛКИХ И КРУПНЫХ СОСУДОВ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

Inass Shaltout[1], Mary Wadie[1], Mazen Attia[1], Aya Khafagy[2], Sarah A. Hassan[1]

[1] — Faculty of Medicine, Cairo University, Cairo, Egypt
[2] — Students' Hospital, Cairo University, Cairo, Egypt

Correlation Between Microvascular and Macrovascular Affection in Type 2 Diabetes Mellitus

Резюме

Цель работы: изучить возможную взаимосвязь между макрососудистыми заболеваниями, особенно атеросклерозом, и нарушениями микроциркуляции у пациентов с СД2, а также оценить взаимосвязь между уровнем глюкозы крови и поражением мелких и крупных сосудов. **Пациенты и методы**: В исследовании приняло участие 150 пациентов: 100 пациентов с СД2 и контрольная группа из 50 участников. Все участники прошли сбор анамнеза и клиническое обследование, а также сдали кровь на биохимический анализ, включая определение уровней гликированного гемоглобина (HBA1c), глюкозы плазмы натощак (FPG), постпрандиального уровня глюкозы через 2 часа (2h-PG), триглицеридов (TG), общего холестерина (TC), ЛПВП и ЛПНП. Видео-капилляроскопию ногтевого ложа (NVC) проводили с целью оценить морфологию капилляров ногтевого ложа, диаметр артерий и вен, изменения длины капилляров и размер петли, наличие или отсутствие капиллярного кровотечения, кровоподтеков, рубцевания, дефектных и крупных капилляров. Для оценки таких изменений использовали полуколичественную шкалу (0–3). Все участники прошли дуплексное исследование сонной артерии для измерения толщины слоя интима-медиа в общей сонной артерии (ТИМ). **Результаты.** Пациенты с СД2 имели существенно большее значение ТИМ по сравнению с контрольной группой. Отмечались более частые случаи отклонений в морфологии капилляров, кровотечений, рубцевания и дефектов капилляров. Модифицированный балл NVC у пациентов с СД2 составил >1 по сравнению с контрольной группой. Кроме того, у пациентов с СД2 наблюдались более высокие показатели частоты кровоподтеков, разветвлений, пересечений и штопоровидных капилляров, большие петли и укорочение капилляров. Зарегистрировано значительное увеличение значений ТИМ слева и справа в группе участников с СД, а модифицированный балл NVC составил >1. **Заключение.** Отмечена тесная связь между атеросклерозом и нарушением микроциркуляции. Видео-капилляроскопию можно использовать для оценки нарушений микроциркуляции до обнаружения атеросклероза по результатам дуплексного исследования сонной артерии.

Ключевые слова: *диабет, видео-капилляроскопия ногтевого ложа, дуплексное исследование сонной артерии, атеросклероз, микроциркуляция*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Исследование одобрено этическим комитетом учреждения (медицинский факультет, Каирский университет (Египет) — Протокол № 132701-2019). Все участники предоставили согласие на участие в исследовании.

Ограничения исследования

Рекомендуется проводить исследование в большей группе для лучшего понимания и корреляции с ретинопатией как микрососудистым осложнением. Кроме того, требуется последующее наблюдение для лучшей оценки взаимосвязи между микроциркуляторными изменениями и макрососудистыми осложнениями.

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Abstract

Aim of the work: to explore the possible relation between macrovascular disease especially atherosclerosis and microcirculation abnormalities in patients with T2DM and, to assess any relationship between blood glucose level, microvascular and macrovascular affection. Patients and methods: the study recruited 150 participants; 100 patients with T2DM and 50 controls. All participants underwent history taking, clinical examination, biochemistry testing including HBA1c, FPG, 2h-PG, TG, TC, HDL, and LDL. Nailfold video capillaroscopy (NVC) was performed to evaluate morphology of the nailfold capillaries, arterial and venous limb diameter, alteration in Capillary length and loop diameter, presence or absence of capillary hemorrhage, extravasation, scarring, scanty and large capillaries. To score these alterations, a semi-quantitative rating scale (0–3) was used. Carotid duplex was done to all participants to measure the intima media thickness in the common carotid artery (CIMT). Results: Subjects with T2DM showed significantly increased CIMT when compared with controls. There were a significantly higher frequencies of abnormal capillary morphology, hemorrhage, scarring and scanty capillaries, Modified NVC score>1 in T2DM. In comparison to the control group, they also exhibited noticeably greater rates of extravasation, branching, crossed, and corkscrew-shaped capillaries, larger loops, and decreased capillary length. There was significantly higher left and right CIMT in the group of diabetics with Modified NVC score >1. Conclusion: A significant relationship was found between atherosclerosis and microcirculation abnormalities. Videocapilloroscopy could be used to assess microcirculatory abnormalities before detection of atherosclerosis by carotid duplex.

Key words: *diabetes, nailfold videocapillaroscopy, carotid duplex, atherosclerosis, microcirculation*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The study was approved by the institutional ethics committee (Faculty of Medicine, Cairo University (Egypt) Protocol No. 132701-2019). All participants provided consent to participate in the study.

Limitations

A larger study group is advised for better understanding and correlation with retinopathy as a microvascular complication, also follow up is needed for better assessment of the relation of microcirculatory changes and macrovascular complications.

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ADA: American Diabetes Association, ASE: American Society of Echocardiography, BMI: Body mass index, CIMT: Carotid intima media thickness, DPP4i: dipeptidyl peptidase 4 inhibitors, EDV: End Diastolic Velocity, ESC: European Society of Cardiology, FBG: Fasting blood glucose, HBA1c: Hemoglobin A1c, HDL: High density lipoprotein, 2h-PG: 2-hour postprandial blood glucose, HTN: Hypertension, ICA: Internal carotid artery, LDL: Low density lipoprotein, Lt: Left, NVC: Nailfold videocapilloroscopy, OGTT: Oral glucose tolerance test, PSV: Peak Systolic Velocity, RBS: Random blood sugar, RI: Resistive index, Rt: Right, T2DM: Type 2 Diabetes mellitus, SD: Standard deviation, TC: Total cholesterol, TG: Triglycerides, WC: Waist circumference

Introduction

T2DM is a metabolic disorder that affects quality of life and represents a burden on society because it is accompanied with many complications mainly vascular complications [1].

About one-third to one-half of diabetic patients experience vascular complications, which can be classified as macrovascular or microvascular). These complications cause damage and failure of various organs [2].

Hyperglycemia is the main cause of microvascular and macrovascular affection. Both types of vascular complications seem to be interconnected but the relation between microvascular, macrovascular complications and chronic hyperglycemia is not clear yet [3].

The artery disease known as atherosclerosis is typified by the buildup of fatty plaques on the inner walls of the vessels. It takes many years for it to develop. Atherosclerotic vascular alterations are linked to both macrovascular and microvascular diabetes problems. B-mode ultrasound is used to measure CIMT, a non-invasive marker of subclinical atherosclerosis. Numerous research has demonstrated a link between CIMT and atherosclerosis [4].

The aim of this work was to explore the possible relation between macrovascular disease variables and microcirculation abnormalities in patients with T2DM. Also, to assess any relationship between blood glucose level, microvascular and macrovascular affection.

Patients and methods

The study recruited 150 participants from the outpatient clinic of DM at Kasr Alainy teaching Hospital divided into two groups age and sex matched: control group which included 50 healthy individuals, and T2DM group which included 100 patients suffering from T2DM based on the ADA criteria diagnosed for at least one year.

The T2DM group was further divided according to glycemic control into two groups, one with HBA1c<7 and the other one with HBA1c>7; to study the relation between glycemic control and microcirculatory changes.

T2DM group was also subdivided into dyslipidemic and non dyslipidemic group to assess the role of dyslipidemia in microcirculatory changes.

Sample size was calculated using STATA 16.

All participants underwent complete medical history taking, thorough clinical examination , biochemical testing was done including HbA1c (%), FPG (mg/dL), 2h-PG (mg/dl) TG (mg/dL), Total Cholesterol (TC) (mg/dL), HDL (mg/dL), and LDL (mg/dL),Imaging in the form of nailfold Capillaroscopy to detect microvascular affection, and carotid doppler ultra-sonography to detect macrovascular affection. They study follows the principles outlined in the Helsinki Declaration of 1964 and its later amendments. The study was approved by institutional ethical committee (faculty of Medicine, Cairo University, Egypt, 2019). A consent was taken from the participants.

Inclusion criteria included adult patients above 30 years old with type 2 diabetes diagnosed for at least one year based on American Diabetes Association criteria [5] as follows: a FPG level of ≥ 126 mg/dL, a 2-h Plasma Glucose (2h-PG) level of ≥ 200 mg/dL in the 75-g OGTT, or a RBG level of ≥ 200 mg/dL and/or HbA1c level ≥ 6.5 %.

Exclusion criteria were any evidence of cancer, active liver disease, current pregnancy, active infection, very poorly controlled heart disease, pulmonary disorders, current or previous tobacco smoking or severe impairment of the renal function, individuals with injuries within the nail fold as a result of aesthetic procedures or nail polish, as well as those exhibiting symptoms of any vascular collagen disease.

None of the patients previously received antihypertensive or lipid lowering drugs.

A nailfold Capillaroscopy examination was performed on each participant utilising a video Capillaroscopy. The optical microscope was connected to a digital camera and computer.

The participant sat calm on the chair in front of the machine. The procedure was explained for him. To increase the translucency, a drop of immersion oil was applied to the finger's nail fold.

The following capillaroscopic properties were evaluated for every image: morphology of the nailfold capillaries (considered normal when there is uniform distribution of capillaries resembling hairpins (comb-like structure) morphological anomalies include branched capillaries, cork screw, and crossed), large capillary (defined by Marique's as 4-10 increase in capillary size and The diameter of the arterial and venous limbs ranges from 7 to 17 μm and 11 to 20.6 μm, respectively, while the capillary width of expanded capillaries is at least 90 to 150 μm (0.090 to 0.150 mm), alteration in Capillary loop diameter (normal values 8 to 14 μm, enlarged loop > 20 μm,), alteration in Capillary length (normal length 200 to 500 μ and increased length, or reduced length) [6-10] and presence or absence of capillary hemorrhage, extravasation and scarring, scanty capillaries.

According to earlier research, a semi-quantitative grading scale was used to grade these modifications [6] score 0, no significant changes, score 1, few (< 4 alterations), score 2, some (between 4 and 6 alterations) and score 3, frequent (> 6 alterations/linear mm).

We categorized our subjects in 2 groups: modified NVC score >1: includes Patients with abnormal capillaroscopic pattern with existence of ≥ 4 abnormal parameters (score 2,3) and modified NVC score ≤ 1comprises individuals who have a uniform distribution of comb-like, hairpin-shaped capillaries and no discernible alterations (score 0).

Participants with suspicious capillaroscopic pattern (score 1) with existence of ≤ 3 abnormal parameters (non-specific morphological abnormalities) [6, 12-14].

Numerous research studies have demonstrated that a microcirculation score more than one indicates a clinically severe impairment [6, 12, 13, 15].

Modified nailfold video capillaroscopy (NVC) attributes were quantified using the NVC score in accordance with a number of criteria.

The report by Barchetta et al. is where the scoring standards were adjusted [6]. All collected data were then documented and subjected to statistical analysis.

An HD5000 system (Philips Ultrasound, Bothell, Washington) equipped with a 7.5- megahertz (MHz) linear array probe to assess the maximum thickness of IMT and a 5-MHz linear array probe to assess the RI of ICA was used to perform the duplex sonographic evaluation.

The patient was lying flat in bed. The IMT was measured in the common carotid artery 2 cm just before common carotid artery bifurcation and also common and internal carotid arteries were screened for any atherosclerotic plaques. Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV) were be calculated of both internal carotid arteries [16].

Spectral analysis: This makes it possible to estimate the blood flow rate, After inserting a probing cursor into the artery (on the screen), a signal indicating the blood flow velocity was produced. There was an audible and visual cue. The systolic and diastolic blood flow are represented by the peaks and ebbs in the signal. The spectrum k15] is made up of the peaks and ebbs [17].

Every asymptomatic adult or hypertensive patient at moderate risk for cardiovascular disease should have their intima-media thickness (IMT), a measure of subclinical atherosclerosis (asymptomatic organ damage), assessed. Values of intima-media thickness exceeding the 75th percentile (ASE) or 0.9 mm (ESC) ought to be regarded as abnormal.

Two of the three criteria—abnormal wall thickness (defined as C-IMT >1.5mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent artery wall border), and abnormal wall texture (brighter echoes than adjacent boundaries)—were used to determine whether plaque was present or not [18].

Statistical analysis: IBM SPSS, Chicago, USA's SPSS statistics software package, version 22.0, was used to conduct statistical analyses. Categorical variables were reported as frequencies and percentages, while continuous data were given as the mean with the standard deviation. The chi-squared test or Fisher's exact test was used to analyse categorical variables, while the Mann-Whitney U test and Student's t-test was used to analyse continuous variables in order to compare the characteristics of the two groups.

Results

In this study, 100 T2DM patients were involved; 88 of the patients were female and 12 were male, with a mean age of 52.4 ± 8.8 (F:M 7:1). The gender (five males and forty-five females; F:M 9:1; p=0.7) and mean age (54.1-20.3) of the 50 controls ranged from 33 to 70 years (p=0.2). The mean duration of this disease in T2DM group was 8 years (mean± SD= 8.5± 7.1 years). When compared to the control group, the T2DM group has significantly greater FPG, 2h-PG, HbA1c, TC, LDL, TG, and reduced HDL. The CIMT measurements showed a statistically significant difference between the T2DM patients and the controls, with higher values (mean 0.1 ± 0.02, p value 0.00) (Table 1).

Table 1. *Clinical and biochemical characteristics together with CIMT measurements of T2DM group and control group*

Characteristics	T2DM	Controls	P Value
	n = 100	n = 50	
Age (years)			
Range	33 — 70	33 — 70	
Mean ± SD	52.4 ± 8.8	54.1 ± 9.3	0.268
Gender			
Male	12 (12 %)	5 (10 %)	0.716
Female	88 (88 %)	45 (90 %)	
WC (cm)			
Range	78 — 138	77 — 138	
Mean ± SD	108.5 ± 9.9	105.6 ± 12.1	0.112
BMI			
Range	21.3 — 55	22.9 — 52	
Mean ± SD	36.7 ± 6.8	35.2 ± 6.6	0.193
HTN	31 (31 %)		
Duration of Disease (years)			
Range	1 — 35		
Mean ± SD	8.5 ± 7.1		
DM Treatment			
Insulin	40 (40 %)		
Oral hypoglycemic	37 (37 %)		
Sulphonylureas	30		
DPP4i	7		
Insulin + oral hypoglycemic	23 (23 %)		
Insulin+DPP4i	7		
Insulin+sulphonylureas	16		
FPG (mg/dL)			
Range	65 — 359	61 — 114	
Mean ± SD	174.5 ± 60.9	85.5 ± 9.6	**<0.001**
2h-PG (mg/dL)			
Range	110 — 649	90 — 161	
Mean ± SD	290.9 ± 99.4	120.4 ± 14.6	**<0.001**
HbA1c (%)			
Range	5.1 — 12.3	4.9 — 6.4	
Mean ± SD	8.7 ± 1.3	5.8 ± 0.5	**<0.001**
TC (mg/dL)			
Range	102 — 493	112 — 199	
Mean ± SD	230.7 ± 70.6	159.9 ± 30.2	**<0.001**
HDL (mg/dL)			
Range	26 — 69	40 — 60	
Mean ± SD	42.9 ± 9.9	51.4 ± 5.9	**<0.001**
LDL (mg/dL)			
Range	20 — 423	20 — 129	
Mean ± SD	140.9 ± 65.7	96.4 ± 22.4	**<0.001**
TG (mg/dL)			
Range	68 — 764	54 — 149	
Mean ± SD	213.3 ± 130.1	99.2 ± 25.1	**0.003**
Lt. CIMT (cm)			
Range	**0.06 — 0.3**	**0.05 — 0.12**	
Mean ± SD	0.1 ± 0.03	0.08 ± 0.02	**<0.001**
Rt. CIMT (cm)			
Range	0.07 — 0.2	0.06 — 0.12	
Mean ± SD	**0.1 ± 0.02**	**0.08 ± 0.01**	**<0.001**
Atherosclerosis	70 (70 %)	16 (32 %)	**<0.001**

Note. WC — Waist circumference, BMI — Body Mass Index, HTN — hypertension, DM — diabetic mellitus, FPG — Fast-post glucose, 2h-PG — Postprandial plasma glucose at two hours, TC — total cholesterol, HBA1c — haemoglobin A1c, HDL and LDL — High and Low densiy Lipoproteins, TG — Triglycerides, CIMT — The thickness of the carotid intima media, Rt — right, Lt — left, DPP4i — dipeptidyl peptidase 4 inhibitors

When comparing the T2DM group to the control group, there is a statistically significant increase in the incidence of aberrant capillary morphology, scarring, capillary haemorrhage, and sparse capillaries (p values <0.001, 0.001, 0.005, and 0.03 correspondingly). They also had higher frequency of Branched capillaries, extravasation of capillaries, crossed capillaries, corkscrew shape capillaries, reduced capillary length, enlarged Loops when compared with control group, but these changes didn't reach statistical significance (p value 0.17, 0.553, 0.551, 0.551, 0.454, 0.719 respectively). In T2DM group, there was 19 % of patients had scarring in the capillary field, 14 % had capillary hemorrhage, and 10 % had scanty capillaries and all these findings did not present at all in control group, so it cannot be considered as a normal variant. The control group has a significantly higher frequency of Modified NVC score ≤ 1 when compared with T2DM group. (Table 2, Figure 1).

There was no discernible variation in CIMT and NVC measures, morphological alterations, or statistical significance between the HbA1c ≥ 7 and the HbA1c < 7 groups in individuals with T2DM, but we noticed reduced NVC measurements in the HbA1c ≥ 7 group when compared with the HbA1c < 7 group in patients with T2DM. They have also higher frequency of scarring, capillary hemorrhage, scanty capillaries, large capillaries, branched capillaries, extravasation of capillaries and crossed capillaries when compared with the other group (Table 3).

The dyslipidemic group had a significantly higher FPG, 2h-PG, and HbA1c when compared with the non dyslipidemic group. There was a significantly higher frequency of HbA1c < 7 in the non dyslipidemic group when compared with dyslipidemic group, but no statistically significant difference between dyslipidemic and the non dyslipidemic group in patients with T2DM regarding CIMT measurements (Table 4).

Table 2. *NVC measurements of T2DM group and Control group*

	T2DM group	Control group	P value
Arterial Limb (μm)			
Range	4 — 13.9	4.1 — 16.1	
Mean ± SD	9.67 ± 2.72	9.04 ± 2.54	0.186
Venous Limb (μm)			
Range	10.4 — 19.2	8.06 — 24	
Mean ± SD	15.52 ± 2.57	14.39 ± 3.34	0.087
Capillary Loop (μm)			
Range	9.2 — 27.9	6 — 30.2	
Mean ± SD	18.58 ± 5.44	18.01 ± 5.17	0.582
Capillary Length (μm)			
Range	95.7 — 283.3	78.7 — 284.4	
Mean ± SD	162.69 ± 49.4	156.93 ± 44.1	0.619

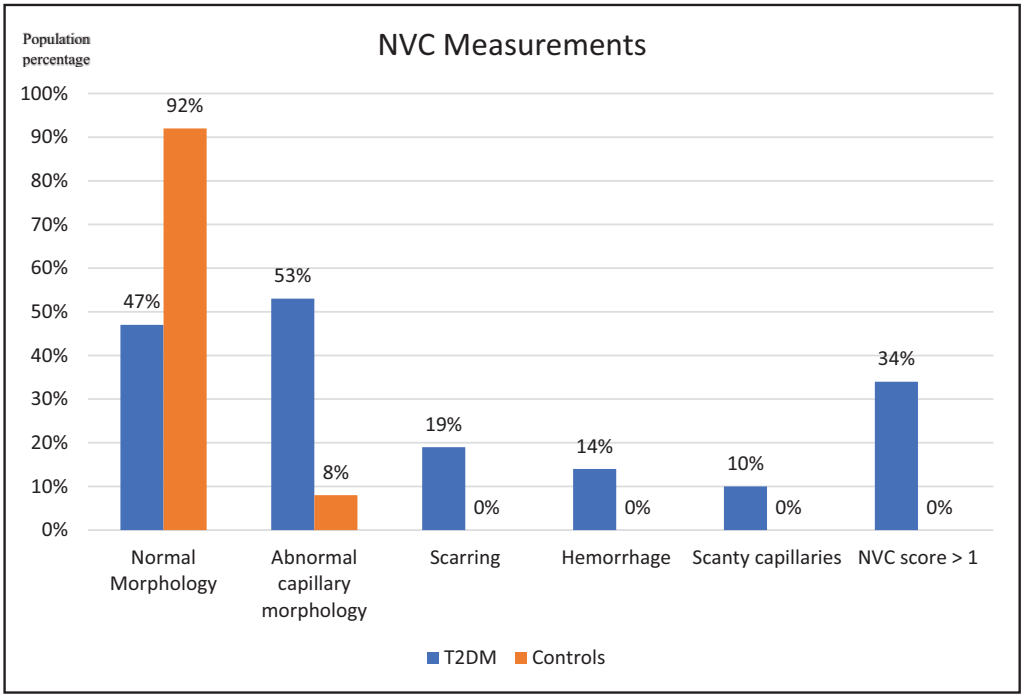

Figure 1. *Shows frequency of NVC measurements in T2DM group and control group*

Table 3. *Comparison of CIMT and NVC measurements between the HBA1c < 7 and HBA1c ≥ 7 groups in T2DM group*

Characteristics	HbA1c < 7	HbA1c ≥ 7	P Value
	n = 15	n = 85	
Lt. CIMT (cm)			
Range	0.07 — 0.13	0.06 — 0.3	
Mean ± SD	0.1 ± 0.02	0.1 ± 0.03	0.224
Rt. CIMT (cm)			
Range	0.08 — 0.13	0.07 — 0.2	
Mean ± SD	0.09 ± 0.03	0.1 ± 0.02	0.517
Atherosclerosis (%)	11 (73.3 %)	59 (69.4 %)	1.000

Note. HbA1c — hemoglobin A1c, CIMT — carotid intima media thichness, Rt — right, Lt — left

Table 4. *Comparison of clinical and biochemical characteristics between the dyslipidemic and non-dyslipidemic groups in T2DM group*

Characteristics	Dyslipidemic	Non-dyslipidemic	P Value
	n = 91	n = 9	
Age (years)			
Range	33 — 70	54 — 62	
Mean ± SD	51.9 ± 8.9	57.8 ± 3.6	**0.029**
Gender			
Male	11 (12.1 %)	1 (11.1 %)	1.000
Female	80 (87.9 %)	8 (88.9 %)	
WC (cm)			
Range	78 — 138	91 — 122	
Mean ± SD	108.5 ± 10.1	108.9 ± 8.8	0.838
BMI			
Range	21.3 — 55	28.3 — 51.2	
Mean ± SD	36.5 ± 6.7	39.2 ± 7.2	0.268
HTN	28 (30.8 %)	3 (33.3 %)	1.000
Duration of Disease (years)			
Range	1 — 35	1 — 20	
Mean ± SD	8.5 ± 7.1	9 ± 6.8	0.740
DM Treatment			
Insulin	34 (37.4 %)	6 (66.7 %)	0.151
Oral hypoglycemic	35 (38.5 %)	2 (22.2 %)	0.478
Insulin + oral hypoglycemic	22 (24.2 %)	1 (11.1 %)	0.680
FPG (mg/dL)			
Range	65 — 359	90 — 178	
Mean ± SD	178.7 ± 61.5	132.7 ± 34.5	**0.019**
2h-PG (mg/dL)			
Range	110 — 649	140 — 290	
Mean ± SD	298.9 ± 99.3	210.2 ± 56.1	**0.005**
HbA1c (%)			
Range	5.1 — 12.3	6.2 — 10.7	
Mean ± SD	8.8 ± 1.2	7.7 ± 1.6	**0.038**
HbA1c			
< 7	10 (11 %)	5 (55.6 %)	**0.003**
≥ 7	81 (89 %)	4 (44.4 %)	
Lt. CIMT (cm)			
Range	0.06 — 0.3	0.07 — 0.12	
Mean ± SD	0.1 ± 0.03	0.1 ± 0.02	0.513
Rt. CIMT (cm)			
Range	0.07 — 0.2	0.08 — 0.13	
Mean ± SD	0.1 ± 0.02	0.1 ± 0.02	0.815
Atherosclerosis	64 (70.3 %)	6 (66.7 %)	1.000

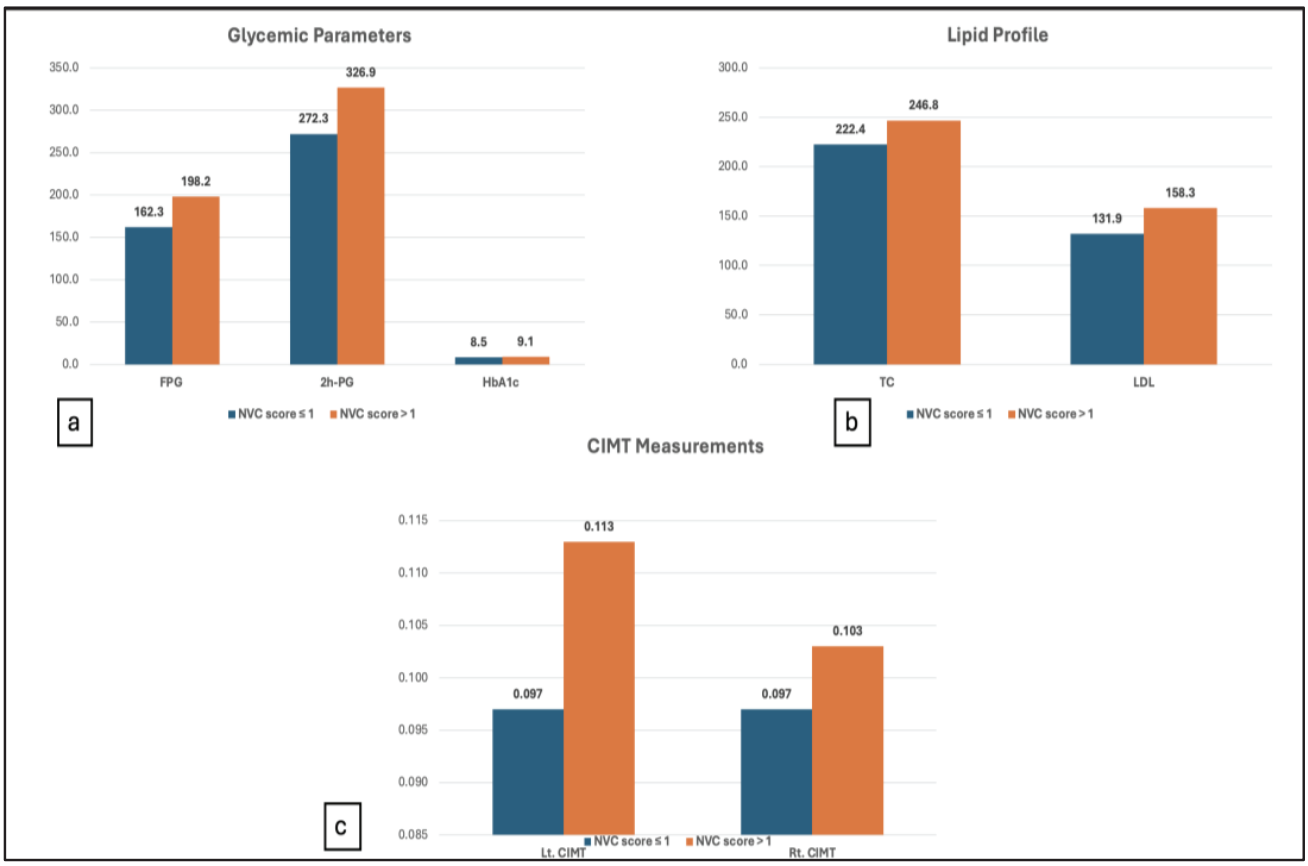

Figure 2. *Comparison between modified NVC score ≤ 1 and modified NVC >1 groups in T2DM patients as regards glycemic parameters (a), lipid profile (b) and right and left CIMT measurements(c)*

When comparing the group of type 2 diabetics with a Modified NVC score of ≤1 and those with Modified NVC score>1, FPG, 2h-PG, HbA1c, TC, and LDL all showed statistically significant increases, Lt and Rt CIMT measurements all showed statistically significant increases in the diabetics group with a Modified NVC score of >1 (figure 2).

Lt. CIMT was found to have a statistically significant direct association with age, TC, and LDL. Table 5 indicates that there was no statistically significant link discovered between CIMT measures and NVC measurements, although there was a statistically significant direct correlation between Rt. CIMT and age.

Discussion

Atherosclerosis in diabetic patients is a complex process which is the result of interaction of many factors, not only dyslipidemia, and total cholesterol and LDL are the most important parameters that affect vascular affection. The development of atherosclerosis was substantially correlated with increasing age. Thus, the ageing process that leads to atherosclerosis happens over a long period of time.

In our study we found that Rt. and Lt. CIMT were significantly higher in T2DM patients when compared to controls and this emphasize the hypothesis of premature atherosclerosis that occurs in diabetic patients despite that both groups had visceral obesity.

This is in line with the findings of Brohall G et al., who discovered that patients with diabetes mellitus had noticeably higher CIMT levels than healthy persons [19].

In our study there was a significantly abnormal capillary morphology in diabetic patients compared to controls in the form of capillary hemorrhage, scarring and branched capillaries, crossed capillaries, corkscrew shape capillaries, scanty capillaries and extravasation. In addition, type 2 diabetics had significantly higher frequencies of reduced capillary length and enlarged loops than the control group. There is also a significantly higher frequency of Modified NVC score ≤ 1 in controls when compared with T2DM group which signifies microvascular affection in diabetic patients, also we raise the hypothesis that the three morphological changes which are scarring, scanty capillaries and capillary hemorrhage never to be considered as normal variants as their incidence in controls is 0 %.

This is in line with the findings of Po-Chi Hsu et al., who reported that, in comparison to the controls patients, those with pre-DM or T2DM had considerably greater rates of microcirculation abnormalities and altered NVC scores [20].

Table 5. *Correlations between CIMT measurements with clinical and biochemical characteristics and NVC measurements.*

Characteristics		Lt. CIMT	Rt. CIMT
Age	R	0.302	0.286
	p value	**0.002**	**0.004**
W.C.	R	-0.053	0.120
	p value	0.601	0.236
BMI	R	-0.102	0.036
	p value	0.314	0.719
Duration of Disease	R	0.052	0.172
	p value	0.610	0.086
FPG	R	-0.033	-0.051
	p value	0.742	0.615
2hr-PG	R	-0.018	0.051
	p value	0.856	0.616
HbA1c	R	-0.019	0.006
	p value	0.849	0.953
TC	R	0.284	0.103
	p value	**0.004**	0.309
HDL	R	0.029	-0.044
	p value	0.776	0.665
LDL	R	0.253	0.077
	p value	**0.011**	0.447
TG	R	-0.057	-0.043
	p value	0.575	0.669
Arterial Limb	R	**-0.175**	**-0.154**
	p value	0.081	0.127
Venous Limb	R	0.028ab	0.065
	p value	0.779	0.521
Capillary Loop	R	-0.135	0.015
	p value	0.181	0.882
Capillary Length	R	-0.018	0.094
	p value	0.862	0.350

There was no significant difference regarding the CIMT measurements of patients with type 2 DM according to HbA1c level (HbA1c≥7 % and HbA1c<7 %). This may highlight that the process of atherosclerosis is an ongoing process which is not only related to disease control, but it may be related to other parameters in diabetic patients which need further studies.

High HbA1c and elevated CIMT were reported to be significantly correlated in the diabetic investigations by Mukai N et al. [21- 25], However, HbA1c and CIMT results [25] did not significantly correlate in research by Du HW et al. on diabetic mellitus patients.

This difference in results may be due to other factors that affect atherosclerosis like age, hyperlipidemia, duration of disease or even genetic factors. Study size and ultrasound method also may have a role e.g.: our study size is 150 subjects, while Mukai N et al have 2702 subjects the definition of carotid wall thickening also may vary e.g.: in our study it was defined as a maximum IMT of > 0.09 cm, while Mukai N et al defined it as a maximum IMT of >1.0 mm [19]. This also may be due to level of FPG, 2h PP in our patients who were not controlled even in those with HbA1c < 7 %.

The NVC characteristics of patients with type 2 diabetes mellitus were not significantly different between groups based on HbA1c level (HbA1c ≥ 7 % and HbA1c < 7 %). However, we did find that subjects with HbA1c ≥ 7 % had a higher frequency of Modified NVC score > 1, as well as scarring, capillary haemorrhage, large, branched, crossed capillaries, and extravasation.

Nevertheless, upon conducting a quantitative and qualitative analysis of the nailfold capillary abnormalities in type 2 diabetics and classifying them based on Modified NVC score (NVC ≤ 1 and NVC >1), we discovered that the diabetics with Modified NVC score >1 exhibited significantly higher levels of FPG, 2hr-PG, and HbA1c.

These findings suggested that in T2DM patients, alterations of the nailfold capillaries have been linked to poor glycaemic control.This may raise the hypothesis that tight glycemic control will affect microvascular changes before it conducts an effect on macrovascular changes and the first abnormality is the capillary morphology, this may explain that macrovascular complications will take more time to improve than microvascular complications and need more time of tight blood sugar control and may be the etiology of the absence of difference in intima media thickness between controlled and non-controlled patients.

According to Po-Chi Hsu et al, patients with HbA1c≥7 % showed a significantly higher NVC score. Subjects with HbA1c ≥ 7 % [21] had higher rates of shortened capillary length, irregular capillary distribution, abnormal capillary morphology, expanded loop, and abnormal flux.

In our study, no significant difference regarding to The CIMT was found in patients with type 2 DM classified according to lipid abnormalities and this highlights the hypothesis that atherosclerosis in diabetic patients is related not only to dyslipidemia but also to underlying process of inflammation and advanced glycation.

However, Lt. CIMT was proven to have a significant direct correlation with TC and LDL .This finding confirm that the process of atherosclerosis in diabetic patients is complex, and it is due to an interaction of many factors, one of them is dyslipidemia and mainly affected by TC and LDL and that the protective effect of HDL is not enough to protect our diabetic patients from the process of atherosclerosis, which needs a multidisciplinary approach to control it.

We found variables like age, FPG, 2hr-PG and HbA1c significantly higher in dyslipidemic than non dyslipidemic group.

Age, the length of diabetes, systolic and diastolic blood pressure, total cholesterol, triglycerides, LDL cholesterol, FPG, 2-hour postprandial glucose, and HbA1c were among the factors that Sunil et al. showed to have a significant and positive correlation with CIMT, while HDL cholesterol showed a negative correlation with the latter [26].

However, when we categorized type 2 diabetics according to Modified NVC score (NVC ≤ 1 and NVC >1), we found significantly higher levels of TC and LDL in the group of diabetics with Modified NVC score >1. This indicated that nailfold capillary abnormalities have been associated with dyslipidemia (mainly abnormalities in TC and LDL).

There were significantly higher Rt. CIMT and Lt. CIMT in the group of diabetics with Modified NVC score > 1 and so higher frequency of atherosclerosis in this group, so macrovascular abnormalities are more frequent in patients with abnormal capillaroscopic findings, and this means that microvascular and macrovascular complications are correlated to each other and that microvascular affection precedes macrovascular affection.

All these findings emphasize the importance of microvascular study in diabetic patients which may be an early detector for glycemic control in those patients and it is an easy non-invasive method to detect early changes in microvascular affection and an indicator for macrovascular affection.

Conclusion

We emphasized that glycated hemoglobin level affects earlier microvascular complications ealier than macrovascular complications which take longer duration.

Our study also emphasized the hypothesis of premature atherosclerosis among subjects with T2DM and revealed that NVC identified high frequencies of microvascular abnormalities among those patients. This study highlights the importance of microvascular study as well as macrovascular study.

We recommend that all patients with T2DM should undergo carotid doppler ultra-sonography to detect macrovascular affection as a routine investigation. Nailfold capillaroscopy should be done at earlier stage of diabetes mellitus to detect microvascular affection and for proper control of the disease to improve outcomes and avoid related complications.

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Инасс Шалтоут: Анализ и проверка данных

Мэри Уади: Проведение капилляроскопии и проверка рукописи

Мазен Аттиа: Интерпретация данных

Ая Кхафаги: Сбор данных

Сара А. Хассан: Проверка результатов, написание рукописи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Inass Shaltouta: Analyzing and revising the data

Mary Wadieb: Doing the capilloroscopy and revising the manuscript

Mazen Attiac: Interpretting data

Aya Khafagyd: Collecting data

Sarah A. Hassanc: Revising the results, Writing the manuscript

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Информация об авторах

Инасс Шалтоут — профессор, д.м.н., внутренняя медицина, эндокринология, медицинский факультет Каирского университета, Каир, Египет, e-mail: inassshaltout@hotmail.com

Мэри Уади — профессор, д.м.н., внутренняя медицина, медицинский факультет Каирского университета, Каир, Египет, электронная почта: drmarywadie@yahoo.com

Мазен Аттиа — преподаватель, д.м.н., внутренняя медицина, медицинский факультет, Каирский университет, Каир, Египет, e-mail: mazen_ahmed _attia@kasralainy...

Ая Кхафаги — регистратор, к.м.н., внутренняя медицина, студенческая больница, Каирский университет, Каир, Египет, e-mail: ayakhafagy248@gmail.com

Сара А. Хассан — преподаватель, д.м.н., внутренняя медицина, медицинский факультет, Каирский университет, Каир, Египет, e-mail: dr.sarah88@cu.edu.eg, ORCID ID: https://orcid.org/0000-0001-8705-9811

Author information

Inass Shaltout — Professor, M.D, Internal medicine, endocrinology, Faculty of Medicine, Cairo University, Cairo, Egypt, e-mail: inassshaltout@hotmail.com

Mary Wadie — Professor, M.D, Internal medicine, Faculty of Medicine, Cairo University, Cairo, Egypt, e-mail: drmarywadie@yahoo.com

Mazen Attia — Lecturer, M.D, Internal medicine, Faculty of Medicine, Cairo University, Cairo, Egypt, e-mail: mazen_ahmed _attia@kasralainy...

Aya Khafagy — Registrar, Msc, Internal medicine, Students' Hospital, Cairo University,Cairo, Egypt, e-mail: ayakhafagy248@gmail.com

Sarah A. Hassan — Lecturer, M.D, Internal medicine, Faculty of Medicine, Cairo University, Cairo, Egypt, e-mail: dr.sarah88@cu.edu.eg, ORCID ID: https://orcid.org/0000-0001-8705-9811

— Автор, ответственный за переписку / Corresponding author