Endothelial Dysfunction Evaluated using Photoplethysmography in Patients with Type 2 Diabetes

Castillo-Martínez Lilia1, Ortiz-Suárez Gerson1, Montañéz-Orozco Álvaro1, Orea-Tejeda Arturo1,2, Keirns-Davis Candace2, Davila-Radilla Fernando1, Alcala-Davila Efraín1, Kaufman-Ortega Eric1, Infante-Vázquez Oscar3 and Martinez Memije Raúl1

1Instituto Nacional de Ciencias Médicas y Nutrición “SUN” Mexico City, Mexico
2Massachusetts General Hospital Interpreter Services, Boston, MA 02114, USA
3Institutional Department, Instituto Nacional de Cardiología “ICH”, Mexico City, Mexico

Corresponding author: Orea-Tejeda A, Cardiology Service Coordinator, at Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”, Providencia 1218-A 402 Col. del Valle, Benito Juárez, CP 03100 Mexico City, Mexico. Tel/Fax: (5255) 55-13-93-84; E-mail: oreaartt@gmail.com

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Abstract

Background: Diabetes mellitus (DM) reduces life expectancy by a third, principally because of cardiovascular disease and endothelial dysfunction is considered to be one of the first manifestations of vascular disease. Photoplethysmography is a non-invasive technique to evaluate endothelial dysfunction based on the emission of infra-red light on the skin.

Objective: To evaluate endothelial function by photoplethysmography in patients with type 2 DM without evidence of vascular disease.

Methods: A cross-sectional study of patients with and without DM was undertaken. Endothelial function was evaluated using photoplethysmographic waves taking into consideration the shape of the curve and time of maximum amplitude/total time of the curve (TMA/TT) before and after ischemia induced by arterial obstruction.

Results: In 174 subjects included, a greater basal TMA/TT index was found in diabetics, even after adjusting for age, hypertension, dyslipidemia and hyperthyroidism. The percent change in amplitude post-ischemia compared to basal value was diminished in diabetics (p=0.030). Persons with diabetes, with and with not endothelial dysfunction, had comparable HbA1c concentrations; but diabetics with endothelial dysfunction, had lower serum concentration of HDL-C. (p=0.05)

Conclusions: More endothelial dysfunction was found in patients with diabetes. While the control of diabetes did not influence endothelial dysfunction, it was associated with HDL cholesterol.

Keywords: Endothelial dysfunction; Photoplethysmography; Type 2 diabetes

Introduction

Cardiovascular disorders represent the principal cause of preventable death globally and efforts to early detect cardiovascular disease will definitely contribute to the prevention of it [1]. Type 2 diabetes mellitus (T2DM) includes a group of metabolic abnormalities that share hyperglycemia secondary to a deficit in insulin secretion, a defect in its metabolic activity, or both. Diabetes is associated with chronic vascular, microvascular and/or neuropathic complications. Life expectancy of diabetic patients is reduced by a third; patients with chronic complications have twice the risk of dying than the general population [2,3].

Endothelial cells (EC) through physical and chemical changes induce blood vessels abnormal response to functional adaptations. This is the result of a process of genetic expression, and synthesis and processing of highly regulable proteins. This adaptive capacity gives endothelial cells a key role in the regulation of vascular homeostasis [4].

Some studies have shown the relationship between the PLA2 gene variant and the incidence of major adverse cardiovascular events, a significantly worse prognosis and a higher incidence of cardiac death, AMI, and new myocardial revascularization. As well, in hypertensive patients with cerebrovascular events, the presence of the PLA2 allele was associated with a 4.1 higher risk to develop stroke rather than TIA [5].

Endothelial dysfunction can be defined as an imbalance in the bioavailability of vasoactive substances from the endothelium that precipitate inflammation, vasoconstriction and increase in vascular permeability and that can facilitate the development of arteriosclerosis, platelet aggregation and thrombosis. Known coronary risk factors (e.g., cholesterol combined with low density lipoproteins (LDL-C), smoking, diabetes and hypertension) and other emerging factors (e.g., oxygen free radicals, homocysteine, infections and estrogen deficiency) contribute to endothelial dysfunction [3,5,6].

One of simplest diagnostic tools in use for non-invasive evaluation of the vascular system is photoplethysmography. It is a photometric method that makes use of the optic properties of tissue and blood in a selected area of skin, the exactitude of which has improved with new digital technologies. In this technique an infra-red light is directed...
toward the skin. The amount of light absorbed will depend on the volume of blood in the vessels in the area of exposure. Consequently, a part of the light reflected will correspond to the variations in blood volume and can be measured. However, it is important to bear in mind that only relative measurements are possible; that is, only changes in volume can be captured but not absolute values [7,8].

In 2007 Aldama-Figueroa et al. described the photoplethysmographic wave as the transmission time from the peak systolic pulse volume corresponding to the length of systole and diastole. This indicated a very short rising time of the systolic wave volume. In addition, the rising time in normal subjects reached a maximum value close to 30% of the total duration of the photoplethysmographic wave. Consequently, the signal was asymmetric with a much shorter rising time than falling time. This was the wave they described as normal [8].

In 2005 Manfredi et al. quantified vasodilatation by measuring the percentage of flow (VDMF%). They identified the existence of endothelial dysfunction when the VDMF was less than 10% and severe when it was less than 5%. In a group of primary prevention outpatients, the prevalence of endothelial dysfunction was 66% and was associated with increased thickness of the intima-media [9].

In patients with diabetes mellitus Gargiulo et al. found that their reactive hyperemia index was less than that found in patients without diabetes (1.69 ± 0.388 vs 1.84 ± 0.44; p=0.019). They also observed that both diabetes mellitus and coronary artery disease were associated with endothelial dysfunction. The endothelial dysfunction of diabetics without coronary artery disease was comparable to that of patients with coronary artery disease without diabetes [10]. This cross-sectional study proposes to identify early alterations of endothelial function by photoplethysmography in patients with diabetes and compare them to patients without diabetes.

Material and Methods

The study population was drawn from patients in the outpatient service of the INCNMSZ with type 2 diabetes mellitus (T2DM) who were treated in the Diabetes Clinic (study group) and patients of the Internal Medicine Service without diabetes (control group) between October 2012 and May 2013. Patients received medications for associated conditions as well as treatment for diabetes (both oral antihyperglycemic agents and insulin).

Exclusion criteria included participation in other research protocols, type one diabetes or diabetes caused by pancreatitis or severe liver failure, pregnancy, treatment with stimulation of nitric oxide, uncontrolled thyroid disease, known microangiopathy or macroangiopathy, history of acute myocardial infarction, malignant disease or oncologic treatment, or cardiac arrhythmia that impeded interpretation of the study.

On those patients who voluntarily provided informed consent photoplethysmography was performed in the Heart Failure Clinic of the INCNMSZ. With the patient seated, a tracing of the baseline photoplethysmographic wave was obtained over 30 seconds. Subsequently the ischemic phase was induced using a blood pressure cuff inflated to a pressure 30 mmHg higher than the systolic pressure for 5 minutes. A new photoplethysmographic tracing was registered for 120 seconds immediately after the cuff was deflated (post-ischemic phase). The pulse wave was analyzed at 30 second intervals and compared with baseline values. The following variables were obtained: time of maximum amplitude/total time index (TMA/TT) [11]. This is time from the beginning of the photoplethysmographic wave to the maximum systolic peak (TMA) and the time of the total duration of the wave (TT). These data provided the baseline and post-ischemic TMA/TT indexes [11].

Measurements of the amplitude of the systolic peak of the baseline photoplethysmographic wave and the percent change in amplitude of the wave were calculated at 30, 60, 90 and 120 seconds post-ischemia [9]. Endothelial dysfunction was considered to be present if the post-ischemic wave did not increase at least 10% in comparison to the baseline value. The PPG utilized was a devise designed by the Instrumentation Department at the Instituto Nacional de Cardiología "ICh" with two emitting light diodes, one red of 665 nm and other infrared of 940 nm, with the purpose to attenuate the effects of absorption differences between the oxi and deoxyhemoglobine.

Statistical analysis

The data are presented as absolute and relative frequencies for qualitative variables, and as mean ± standard deviation or median and percentiles (25, 75) depending on whether the data were distributed symmetrically or asymmetrically. For comparison of data between two groups of variables Student’s T or Mann and Whitney’s U tests were used for normal and abnormal distribution, respectively. Qualitative variables were analyzed by Χ2. ANOVA was used for repeated measurements to analyze the percent change of amplitude in time with respect to the baseline measurement. A value of p< 0.05 was considered to be significant. All analyses were performed with the SPSS program for Mac OS X, version 21.0.

Ethical Considerations

The protocol was approved by the Committee of Biomedical Research on Humans of the INCNMSZ.

Results

The population included 174 individuals, 69% of whom were women. The average age in the T2DM group was less than that of controls. The number of histories of arterial hypertension and waist/hips index, as well as alcohol and tobacco consumption, was significantly greater in patients with diabetes mellitus (Table 1).

Table 2 shows the treatment prescribed. Diabetic patients used more beta-blockers and ACE inhibitors. Of the diabetic patients 83% took biguanide antihyperglycemics and 21% sulfonylureas. In patients receiving insulin 48% used intermediate-acting insulin. As far as the blood chemistry variables were concerned (Table 3), as could be expected, the diabetics had higher fasting glucose and HbA1c than the controls, but no statistical difference was found in the concentrations of serum lipids.

In the photoplethysmographic results, the low amplitude of the baseline curve in diabetics was striking, even though this finding only approached statistical significance. The total time of the curve was also less, with a higher baseline TMA/TT index in this group. This finding was statistically significant even after adjusting for age, arterial hypertension, dyslipidemia and hypothyroidism. The other differences were not statically significant.

When diabetic patients with endothelial dysfunction were compared to those without, the only findings of statistical significance were the serum levels of HDL (p=0.05). The rest of the results showed
no difference (Table 4). The percentage of patients with endothelial dysfunction is almost double that of diabetic patients without endothelial dysfunction, a difference that only demonstrated a tendency toward statistical significance (Figure 1). However, when the percent change in amplitude post-ischemia was compared to the baseline curve, it was lower in diabetics (p=0.030) (Figure 2).

In a group of outpatient clinic the prevalence of endothelial dysfunction was 66% and was associated with increased thickness of the intima-media (ITIM) [9]. In the distribution by terciles, patients with DM with ITIM of 0.82 mm had odds ratio (OR) of 4.77, with a 95% confidence interval (CI 95%) of 1.36-16.77, p = 0.001, adjusted to sex and age. When the median was taken as the cut-off point of ITIM, ED had a sensitivity of 71.1% and a specificity of 57.6% for ITIM of 0.76mm. Endothelial dysfunction was also associated with atheromatous plaques (OR 3.66, CI 95% 1.52-8.8; p=0.0001) [9].

The role of calcium/calmodulin-dependent kinases (CaMKs) function in cardiovascular pathophysiology is increasing and is established that CaMKII is an important factor in cardiac response and vascular tone regulation through mechanism that involves eNOS activation and phosphorlylative events. Impairment of CaMK-mediated activation of eNOS, as in CaMK4 gene deletion that induces hypertension demonstrated by the fact that CAMK4/ mice displays a hypertensive phenotype that leads to typical organ damage [14].

Undoubtedly, another factors participate in the vascular tone regulation, is the case of G-protein-coupled receptor kinases (GRKs), which represent one of the largest classes of cell-surface receptors [15]. One of them, the type 2 ryanodine receptor (RyR2) is a Ca$^{2+}$ release channel on the endoplasmic reticulum (ER) of several types of cells, including cardiomyocytes. In these RyR2-dependent Ca$^{2+}$ release is critical for excitation-contraction coupling; endoplasmic reticulum (ER) and mitochondria are highly dynamic organelles that are structurally and functionally related. The activation of ER stress response has been demonstrated to cause mitochondrial dysfunction, triggering oxidative stress and further exacerbating ER stress. These results suggest a scenario in which the chronic ER Ca$^{2+}$ leak triggers ER stress and mitochondrial dysfunction, causing a bioenergetic deficit with decreased ATP synthesis [16].

In 1981 Hecht et al. described abnormalities of cardiac perfusion. In their examination of perfusion, reverse redistribution occurred 7% of their subjects, and 85% of these demonstrated severe coronary artery disease with 90% obstruction. Two thirds of their patients had obstructions greater than 75% and the rest normal coronary arteries. Consequently, reverse redistribution was considered to be a marker of coronary lesion [17].

Association between HF and T2DM is also unclear. Numerous hypotheses have been proposed, including a neurohumoral deregulation, an increased deposition of interstitial myocardial collagen, a higher risk of microvascular dysfunction, and atherosclerosis [18]. The association between HF and T2DM is unclear, have been proposed, as a cause a neurohumoral deregulation, an increased deposition of interstitial myocardial collagen, a higher risk of microvascular dysfunction, and atherosclerosis. Patients receiving insulin might be presumed to present a higher cardiovascular risk compared to those not receiving insulin, although CARE-HF and MADIT-CRT trials have demonstrated similar improvements in LV performance in diabetic and non-diabetic patients [18,19].

In patients with heart failure, Orea-Tejeda et al. [20] found that the administration of L-arginine and citrulline normalized the TMA/TT
index, and this had a positive impact on systemic and pulmonary hemodynamics.

In 2011 Gargiulo et al. reported that in patients with DM the reactive hyperemic index was lower than that of patients without diabetes (1.69 ± 0.38 vs. 1.84 ± 0.44; p = 0.019) and that DM and coronary artery disease were associated with endothelial dysfunction. The rate of endothelial dysfunction in diabetics without coronary artery disease was comparable to that of patients without diabetes but with coronary artery disease [10].

In the present study, the principal findings were that patients with diabetes had greater waist/hips indexes and tobacco use as well as greater prevalence of arterial hypertension and alcohol consumption and lower glomerular filtration rates than the non-diabetics. Their use of medications was greater, particularly beta-blockers and ACE inhibitors. The similar doses of biguanide antihyperglycemiants used were consistent with the elevated BMIs in both groups of diabetics.

The baseline TMA/TT index was greater in patients with diabetes than in control patients. In our population (22,231), an index value less than 30 was considered normal, given that the peak systolic flow to reach its maximum amplitude. As other authors have suggested this may be explained by a diminished secretion of vasodilators and an attenuated response to them in the arterial wall. Thus, even though strict application of the cut-off point we used does not permit us to identify endothelial dysfunction in our subjects, the higher indexes in the diabetic patients strongly suggests incipient alterations of endothelial function.

If we use Manfredi et al. [9] criterion for endothelial dysfunction—the inability to increase the amplitude of the pulse wave post-ischemia more than 10% with respect to the baseline amplitude of the photoplethysmographic curve we find a higher prevalence of endothelial dysfunction in diabetic patients than in controls, although the difference only shows a tendency toward statistical significance. The latter may be the result of the small sample size.

Our findings were similar to those of Gargiulo et al. [10], although in their study the differences were statistically significant. This could have been influenced by the cut-off point they used for endothelial dysfunction (a value less than two standard deviations from the mean of their control patients). We did not feel that this was an appropriate cut-off point for our patients since the controls were not perfectly healthy; they also had pathological conditions that potentially could influence endothelial function.

Diabetic patients with and without endothelial dysfunction had comparable HbA1c values, in contrast to Gargiulo et al. [10] findings. This might have been because the fasting glucose value was similar in the two groups, suggesting that our diabetic population was not adequately controlled. It is noteworthy that there were diabetic patients both with and without endothelial dysfunction; this obliges us to consider that there may be other causal factors of ED.

| Variable               | Diabetics (n = 126) | Non-diabetics (n = 48) | p     |
|------------------------|---------------------|------------------------|-------|
| Women n (%)            | 89 (71)             | 31 (65)                | 0.44  |
| Age (years)            | 63.0 (54.5-69.0)    | 58.5 (44.3-65.0)       | 0.04  |
| BMI (Kg/m2)            | 28.2 ± 4.9          | 28.4 ± 4.7             | 0.72  |
| BSA                    | 1.76 (1.61-1.95)    | 1.78 (1.67-1.96)       | 0.27  |
| Waist (cm)             | 97.3 ± 13.4         | 95.0 ± 14.6            | 0.33  |
| Hips (cm)              | 102.0 (96.0-107.0)  | 104.0 (99.5-109.5)     | 0.21  |
| Waist/hips index       | 0.94 ± 0.08         | 0.91 ± 0.10            | 0.02  |
| Hypertension, n (%)    | 79 (63)             | 18 (38)                | <0.001|
| Hypothyroidism, n(%)   | 37 (29)             | 13 (27)                | 0.76  |
| Dyslipidemia, n (%)    | 73 (68)             | 15 (56)                | 0.24  |
| Alcohol consumption, n (%) | 37 (29)         | 5 (10)                 | <0.001|
| Smoking, n (%)         | 43 (34)             | 19 (40)                | 0.5   |
| Tobacco index (pack-year)| 7.2 (2.3-23.0)    | 2.0 (0.6-6.0)          | 0.05  |
| GFR (ml/min/1.73m2)    | 85.9 ± 30.8         | 99.5 ± 29.5            | 0.06  |
| Renal failure, n (%)   | 19 (19)             | 2 (9)                  | 0.27  |

BMI: Body Mass Index, BSA: Body Surface Area, GFR: Glomerular Filtration Rate. The data are presented as n (%) or mean ± SD or median (25-75)

Table 1: General characteristics, measurements and comorbidities of the total population and in those with or without type 2 diabetes mellitus.
| Variable                  | Population (n=174) | Diabetics (n=126) | Non-diabetics (n=48) | p   |
|---------------------------|--------------------|-------------------|----------------------|-----|
| Beta-blockers, n (%)      | 30 (17)            | 27 (21)           | 3 (6)                | 0.01|
| ACEI, n (%)               | 62 (36)            | 52 (41)           | 10 (21)              | 0.01|
| ARA, n (%)                | 27 (16)            | 22 (18)           | 5 (10)               | 0.25|
| Thiazides, n (%)          | 24 (14)            | 21 (17)           | 3 (6)                | 0.07|
| Loop diuretics, n (%)     | 13 (8)             | 13 (10)           | 0 (0)                | 0.02|
| Ca antagonists, n (%)     | 31 (18)            | 27 (21)           | 4 (8)                | 0.04|
| Statins, n (%)            | 64 (37)            | 51 (41)           | 13 (27)              | 0.1 |
| Aspirin, n (%)            | 69 (40)            | 58 (46)           | 11 (23)              | 0.15|
| Fibrates, n (%)           | 35 (20)            | 30 (24)           | 5 (10)               | 0.04|
| Omega 3, n (%)            | 11 (13)            | 10 (11)           | 8 (11)               | 0.32|
| Levothyroxine, n (%)      | 49 (28)            | 36 (29)           | 13 (27)              | 0.84|
| PPI, n (%)                | 22 (13)            | 14 (11)           | 8 (17)               | 0.32|
| Vitamin D, n (%)          | 16 (9)             | 13 (10)           | 3 (6)                | 0.4 |
| Ca antagonists, n (%)     | 17 (10)            | 12 (10)           | 5 (10)               | 0.85|
| NSAIDs, n (%)             | 10 (6)             | 6 (13)            | 2 (4)                | 0.01|

ACEI: Angiotensin Converting Enzyme Inhibitors, ARAs: Angiotensin 2 Receptor Inhibitors, Ca antagonists: Calcium channel antagonists, PPI: Proton Pump Inhibitors, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs. The data are presented as n (%)

Table 2: Actual medication use of the total population and comparison between those with or without type 2 diabetes mellitus.

| Variable                  | Population (n=174) | Diabetics (n=126) | Non-diabetics (n=48) | p   |
|---------------------------|--------------------|-------------------|----------------------|-----|
| Glucose(mg/dl)            | 117 (92-170)       | 136.5 (96.3-190.0)| 92 (84-95)           | 0.34|
| Creatinine (mg/dl)        | 0.78 (0.66-1.02)   | 0.79 (0.66-1.09)  | 0.77 (0.65-0.88)     | 0.36|
| HbA1c (%)                 | 7.9 (6.5-9.7)      | 8.2 (6.8-10)      | 5.7 (5.5-6.0)        | <0.001|
| Serum Albumin (g/dl)      | 4.4 (4.1-4.6)      | 4.4 (4.1-4.6)     | 4.4 (3.8-4.6)        | 0.8 |
| Total Cholesterol (mg/dl) | 184.8 ± 39.7       | 182.8 ± 36.1      | 195.3 ± 55.0         | 0.34|
| Triglycerides (mg/dl)     | 135.0 (105.3-189)  | 131.0 (106.0-193.0)| 138.5 (93.8-157.3)  | 0.53|
| HDL-C (mg/dl)             | 46.0 (40.0-56.0)   | 45.0 (39.5-54.0)  | 51.0 (40.5-60.0)     | 0.2 |
| LDL-C (mg/dl)             | 105.3 ± 33.0       | 103.3 ± 28.8      | 115.2 ± 49.3         | 0.3 |
| SBP (mmHg)                | 120 (116-130)      | 130 (116-140)     | 120 (112-129)        | 0.004|
| DBP (mmHg)                | 80 (70-80)         | 80 (70-80)        | 80 (70-83)           | 0.02|
| MAP (mmHg)                | 93.3 (83.3-98.3)   | 93.3 (83.3-100)   | 93.3 (85.3-96.7)     | 0.38|

HbA1c: Glycosylated hemoglobin, HDL: High density lipoproteins, LDL: Low density lipoproteins, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure: Mean ± SD, Median (25-75)

Table 3: Biochemical and physiological parameters of the total population and comparison between those with or without type 2 diabetes mellitus.
### Table 4: Comparison of anthropometric, clinical and biochemical findings in diabetic subject with and without endothelial dysfunction.

| Variable                        | With endothelial dysfunction | Without endothelial dysfunction | P     |
|---------------------------------|-----------------------------|----------------------------------|-------|
| Women, n (%)                    | 26 (70.3)                   | 61 (70.9)                        | 0.94  |
| Age (years)                     | 63.0 (53.5-69.0)            | 63.0 (55.0-69.5)                 | 0.97  |
| BMI (Kg/m²)                     | 29.4 ± 4.2                  | 27.5 ± 4.8                       | 0.08  |
| Waist (cm)                      | 99.91 ± 12.08               | 95.44 ± 13.27                    | 0.08  |
| Hips (cm)                       | 103.0 (99.0-112.0)          | 101.0 (96.0-107.0)               | 0.14  |
| Waist/Hips Index                | 0.95 ± 0.09                 | 0.93 ± 0.09                      | 0.22  |
| Diabetes Mellitus 2 (years)     | 15.0 (4.5-22.0)             | 15.5 (7.0-24.0)                  | 0.61  |
| Arterial Hypertension, n (%)    | 51 (59.3)                   | 25 (67.6)                        | 0.38  |
| Hypothyroidism, n (%)           | 22 (25.6)                   | 14 (37.8)                        | 0.17  |
| Dyslipidemia, n (%)             | 48 (65.8)                   | 24 (75.0)                        | 0.4   |
| Alcohol consumption, n (%)      | 24 (27.9)                   | 11 (29.7)                        | 0.83  |
| Smoking, n (%)                  | 28 (32.6)                   | 15 (40.5)                        | 0.39  |
| Tobacco Index (pack-year)       | 7.2 (2.0-25.0)              | 6.9 (2.0-15.0)                   | 0.71  |
| GFR (ml/min/1.73 m²)            | 89.6 ± 28.1                 | 83.5 ± 31.2                      | 0.35  |
| Renal failure, n (%)            | 12 (18.2)                   | 6 (18.8)                         | 0.94  |
| Glucose (mg/dl)                 | 144.0 (93.8-183.3)          | 134.5 (97.0-203.5)               | 0.82  |
| Creatinine (mg/dl)              | 0.79 (0.66-1.02)            | 0.76 (0.66-1.10)                 | 0.93  |
| HbA1c (%)                       | 8.58 ± 1.95                 | 8.43 ± 2.10                      | 0.73  |
| Serum Albumin (g/dl)            | 4.3 ± 0.4                   | 4.3 ± 0.5                        | 0.81  |
| Total cholesterol (mg/dl)       | 183.3 ± 38.7                | 183.6 ± 35.1                     | 0.97  |
| Triglycerides (mg/dl)           | 138 (111-219)               | 127 (104-186)                    | 0.36  |
| HDL-C (mg/dl)                   | 44 (38-50)                  | 48 (41-58)                       | 0.05  |
| LDL-C (mg/dl)                   | 102.7 ± 31.4                | 104.4 ± 27.9                     | 0.79  |
| SBP (mmHg)                      | 122 (110-130)               | 130 (120-140)                    | 0.25  |
| DBP (mmHg)                      | 70 (70-80)                  | 80 (70-80)                       | 0.36  |
| MAP (mmHg)                      | 90.0 (83.3-98.3)            | 93.3 (85.8-100.0)                | 0.29  |

BMI: Body Mass Index, GFR: Glomerular Filtration Rate, HbA1c: Glycosylated Hemoglobin, HDL: High Density Lipoproteins, LDL: Low Density Lipoproteins, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure. The data are presented as n(%), Mean ± Standard Deviation or median (25-75).

In diabetic patients high triglycerides concentrations and reduced C-HDL and LDL’s small and dense are frequent (diabetic dyslipidemia) [23]. As in our population was observed cholesterol-HDL, the levels were lower in patients with ED. This finding agreed with that reported by Toikka et al. [21], who found that flow mediated dilatation was greater in patients with high concentrations of HDL-C in comparison with those with lower concentrations (5.5 ± 3.2 vs. 0.2 ± 1.2% p=0.001), although the diameter of the brachial artery and the increase in flow during hyperemia (454 ± 241 vs. 561 ± 188%, p=0.33) were similar in the two groups. In all subjects flow mediated dilatation correlated with HDL-C (r=0.59, p=0.006). Besler [15] posts that the availability of HDL is important in the production of nitric oxide to inhibit endothelial inflammatory activity and reduce NF-kB activity, the expression of VCAM-1 and monocyte adhesion to the vascular wall, factors that have a significant role in the development and progression of atherosclerosis. In addition HDL induces repair of the endothelium in mice with eNOS deficiency [22]. The results of the present study show that patients with diabetes mellitus have alterations in endothelial function which are evident as a lower increase in the pulse wave amplitude with respect to the baseline.
values in different measurements post-ischemia, compared to patients without diabetes. These findings concur with those of Gargiulo [10] and Manfredi et al. [9]. Although this was to be expected, early detection of ED makes it possible to identify a subgroup of patients with a high risk of cardiovascular disease.

Gargiulo et al.’s [10] group without diabetes but with coronary artery disease had endothelial dysfunction like diabetics with and without coronary artery disease. It is possible to infer that our patients with endothelial dysfunction probably have coronary artery disease, which justifies following them closely and providing treatment before the appearance of symptoms and/or asymptomatic ventricular dysfunction.

Limitations

A special limitation was that heart rate was not considered for to standardize the wave analysis; however we consider that it does not invalid our findings.

In addition, some authors recommend to normalize measurements with the contralateral as control for non-endothelial dependent systemic effects, and it has not been done in this study. However from the Gargiulo et al. [10] study, this result justifies to follow this group of patients and support our findings.

Moreover, gene expression study were not considered in this study, although there are enough information over its roll on endothelial dysfunction.

Conclusion

Patients with diabetes mellitus have diminished endothelial function on the basis of changes in amplitude detected by photoplethysmography. Those with low cholesterol-HDL had the most affected endothelial function. In patients with low concentrations of cholesterol-HDL long term follow-up of endothelial function and its treatment before the appearance of symptoms and/or asymptomatic ventricular dysfunction is justified.

Conflicts of interest

The author(s) declare(s) that there is no conflict of interests regarding the publication of this paper.

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