Insulin Resistance, a Co-factor to Dysglycemia, Predicting Peripheral Neuropathy in Type 2 Diabetic Patients in an Egyptian Population: A Non-Randomized Retrospective Study

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Abstract: Introduction: Insulin Resistance (IR) - a major component of the metabolic syndrome -is directly related to macro-vascular complications in type 2 diabetic patients irrespective of the glycemic level (2). However, the impact of IR on micro-vascular complications such as Diabetic Neuropathy (DN) is not yet fully established. So once more, the IR dilemma rises again but this time from a new prospective. **Material & Methods:** We recruited 120 type 2 diabetic patients diagnosed for a period of less than 3 years, age range (35-65y) 64 females – non-smokers, with no evidence of peripheral arterial disease confirmed clinically and by duplex study. All 120 patients were subject to Clinical Examination, Ezscan / Sudoscan tests & Laboratory investigations – all on a one-day medical service. Laboratory tests included: Glycemic profile (FBG, 2hPPBG & HbA1c). HbA1c was performed both by High-Performance Liquid Chromatography (HPLC) and by capillary blood sample using the Clover system (Boronate Affinity Chromatography, Infopia). 2) Urea, creatinine & microalbuminuria. 3) Lipid profile & Triglyceride. 4) Complete Blood Count & ESR. 5) Liver enzymes ALT & AST. 6) Fasting & PP C-Peptide. 7) C-reactive protein (CRP hs) & Interlukin 6 (IL-6) serum levels, as inflammatory markers. Insulin Resistance was diagnosed by the Ezscan and confirmed by the Homeostatic model assessment (HOMA-2 ir calculator, university of Oxford, 2004) with a cut-off point of >2.5 (for present or absent IR). The results of the Ezscan were categorized as follow: <40% is considered absent IR (HOMA <2.5), from 41-60% is considered mild IR (HOMA 2.6-3), from 61-80% is considered moderate IR (HOMA 3.1-4) and >80% is considered severe IR (HOMA >4). Diabetic Neuropathy (DN) was estimated by the Sudoscan using the micro-Seimens unit (uS) and the results were categorized as follow: (1) Mild DN (green zone, >60 uS). (2) Moderate DN (yellow zone, 40-59 uS). (3) Severe DN (red zone, < 40 uS). **Results:** The results of the Sudoscan & Ezscan tests led to the paradigm of 4 groups: Group A (30 patients, 25%) without evidence of DN and absent IR with an average HbA1c of 8.5% - Group B (42 patients, 35%) with mild DN and mild IR (average 52 %) and average HbA1c of 8.7% - Group C (30 patients, 25%) with moderate DN and moderate IR (average 70 %) and average HbA1c of 7.9% - Group D (18 patients, 15%) with severe DN and severe IR (average 88 %) and average HbA1c of 8.2%. These results were statistically significant (P<0.001) concerning the positive correlation between IR & DN irrespective of HbA1c level a as glycemic marker. A weaker positive correlation could be detected between the level of glycemia (HbA1c) and DN. **Conclusion:** DN is a common incident in most type 2 diabetic patients, it occurs earlier than we expect in the process of the disease. Our study confirms the strong correlation between IR & DN in type 2 diabetic patients irrespective of the severity of symptoms or the glycemic level. It also confirms the accuracy and simplicity of both the Ezscan & Sudoscan as non-invasive and accurate diagnostic tools for IR & DN respectively.

[Ashraf A. El-Sheikh, Nora A. El-Sheikh, Manal M. Badawi, Magda H. Mahran andMaha M. Abdelfattah**. Insulin Resistance, a Co-factor to Dysglycemia, PredictingPeripheral Neuropathy in Type 2 Diabetic Patients in an Egyptian Population: A Non-Randomized Retrospective Study.** *Life Sci J* 2015;12(4s):15-22]. (ISSN:1097-8135). http://www.lifesciencesite.com. 3

Key words: Diabetic Neuropathy, Insulin Resistance, Ezscan, Sudoscan, HbA1c

1. Introduction

Metabolic Syndrome is a cluster of pathological conditions and is considered most dangerous among the cardio metabolic risk factors fueling the cardiovascular epidemic we are facing worldwide (1). Insulin Resistance (IR) - a major component of the metabolic syndrome - is directly related to macro-vascular complications in type 2 diabetic patients irrespective of the glycemi level (2). However, the impact of IR on micro-vascular complications such as Diabetic Neuropathy (DN) is not yet fully established. So Once more the IR dilemma is raised again but this time from a new prospective.

This argument beside our clinical observation powered our desire to evaluate the impact of Insulin Resistance on Diabetic Neuropathy - a major micro-vascular diabetes complication - and to compare as well its effect with that of Hyperglycemia as a predicting and/or a preceding factor for such a serious and disabling medical condition.

If we manage to demonstrate this causative relation between IR and DN we will further raise the awareness of the medical community about this clinical concept often underestimated by many health care professional (HCP) dealing with diabetic patients. We will also encourage the HCP to shift the therapeutic regimen in favor of this direction to target IR when dealing with DN for better clinical outcomes.

This study will try to highlight the significance of IR in comparison to hyperglycemia on DN and weather the latter- in this case- is leading a dominant role with its siblings- dyslipidemia, hypertension and micro-albuminuria - as major risk factors for the Cardio-Metabolic arena.(3)

Our Rational Behind the Selection Criteria

Selected candidates were all type 2 diabetic patients diagnosed within a period of 3 years duration (+/- 6 months). The duration of diabetes was a challenge for our selection because accepting all variables of spectrum of diabetes duration seemed to be confusing for the outcome of our study. Furthermore, the accuracy of diabetes duration is always doubtful in clinical practice, due to the high prevalence of a pre-existing silent diabetes phase of unknown duration in most type 2 diabetic patients.

So we decided to follow the three - year criteria for two main reasons:

1- To assume that eventually all patients would be actual diabetics within a maximum assumption of ten years - respecting the 10 year duration expected occurrence of complications in type 2 diabetes as advised by the ADA,(4)and yet 3 years of diabetes is usually not long enough for hyperglycemia to establish complications.

2- To avoid the "chicken or egg" dilemma of whether diabetes was present with over-imposed insulin resistance, or insulin resistance leads and hyperglycemia follows.

In our study we followed the World Health Organization (WHO)(5) criteria to detect the presence of metabolic syndrome which mainly endorse insulin resistance, rather than just increased waist circumference or obesity with the co-existence of two or more of five abnormalities:

1-Dysglycemia, 2- Hypertension, 3- Hypertriglyceridemia, 4- low HDL, 5- Micro-Albuminuria. Therefore, we measured the five criteria for all of our included subjects.

Insulin Resistance, was measured using both the Ezscan® device and the HOMA-ir calculator.

Ezscan®-(Fig.1)

http://www.impeto-medical.com/clinical-research/completed-studies-width-ezscan/) - this non-invasive, FDA approved, CE marked device is originally designed to predict Diabetes& Pre-Diabetes with an 81% positive predictive value and 94% negative predictive value. It also predict Insulin Resistance (measured in percentage) with a 75% sensitivity and 100% specificity.

As for assessing Diabetic Neuropathy (DN), we used both Clinical assessment (microfilament and vibration test) and the Sudoscan.

Figure 1. Ezscan

This software device detects peripheral &autonomic neuropathy by the measurement of Electro-chemical Skin Conductance (ESC) of the hands and feet using two well-known principles: reverse iontophoresis and electrochemistry. ESC is expressed by micro-Siemens (uS) which is the ratio between the current generated and the constant direct voltage stimulus applied between the electrodes(<4 V).

ESC evaluates local sudomotor function. It reflects the lesions of sympathetic nerve fibers that innervate sweat glands.

These long and small unmyelinated fibers of the autonomic nervous system are the earliest nerve fibers to undergo damage in peripheral diabetic neuropathies(6).

Assessment of symmetry between right & left limbs is also important to differentiate diabetic peripheral neuropathy from other demyelinating neurological diseases or traumatic lesions. http://www.impeto-medical.com/sudoscan-plus/about-sudoscan-plus/.

Measuring micro-albuminuria in the form of urine Albumin to Creatinine ratio (A/C ratio), was suggested as advised by most diabetes organizations and guidelines (7) and is considered an extra tool along with the Sudoscan to further confirm the presence of diabetic microvascular complications.

The Renal State was evaluated by

1. Kidney function tests (serum creatinine and blood urea).
2. The estimated Glomerular Filtration Rate (eGFR) calculated by the equation of Stephen Z. Fadem & Brian Rosenthal.(8)
3. Modification of Diet in Renal Disease (MDRD) calculated by the Sudoscan and confirmed by the equation of Leveym *et al.*(9)

All the laboratory parameters were closely matching and confirmed the results of the Ezscan and Sudoscan with a specificity of 100% and a sensitivity of 85% for both software measurements.

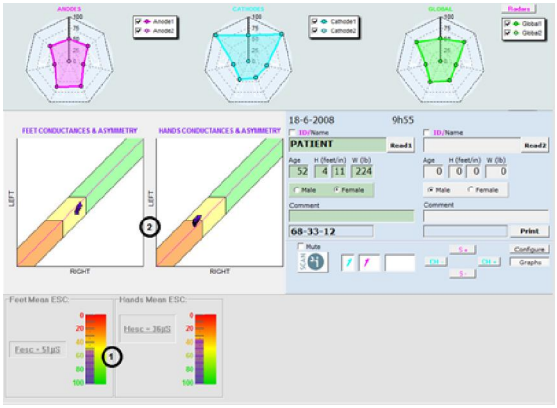

Figure 2: Sudoscan Report

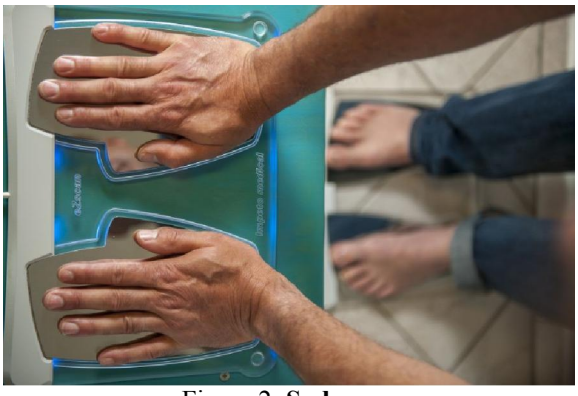

Figure 2: **Sudoscan**

2. Material& Methods

We recruited 120 type 2 diabetic patients diagnosed for a period of less than 3 years, age range 35-65y, 64females – non-smokers, with no evidence of peripheral arterial disease confirmed clinically and by duplex study.

All 120 patients were subjected to Clinical Examination, Ezscan, Sudoscan tests & Laboratory investigations - on a one-day medical service.

Laboratory tests (by Erba Manheim fully automated apparatus) included:

1) Glycemic profile (FBG, 2hPPBG & HbA1c). HbA1c was performed both by High-Performance Liquid Chromatography (HPLC) and by capillary blood sample using the Clover system (Boronate Affinity Chromatography) from Infopia,

2) Urea, creatinine & Albumin / Creatinine ratio (A/C ratio).

3) Lipid profile & Triglyceride (TG).

4) CBC & ESR.

5) ALT & AST.

C-reactive protein (CRP hs) & Interlukin 6 (IL-6) serum levels were measured by the quantitative sandwich enzyme-immunoassay technique (Quantikine ELISA), as inflammatory markers. (10,21).

Insulin Resistance (IR) was diagnosed by the Ezscan as prescribed above and confirmed by the Homeostatic model assessment (HOMA-2 ir calculator, (university of Oxford, 2004) with a cut-off point of >2.5 (for present or absent IR).(11)

The results of the Ezscan were categorized as follow: < 30% is considered absent IR (HOMA <2.5), from 41-60% is considered mild IR (HOMA 2.6-3), from 61-80% is considered moderate IR (HOMA 3.1-4) and >80% is considered severe IR (HOMA >4).

Diabetic Neuropathy (DN) was estimated by the Sudoscan as described earlier and the results were categorized as follow:

- Mild DN (green zone,>60 uS), (Fig.3)
- Moderate DN (yellow zone, 40-59 uS) (Fig.4).
- Severe DN (red zone, < 40 uS). (Fig.5)

Moderate & severe DN results are considered potentially to suffer autonomic diabetic neuropathy as well.

3. Results

The results led to the paradigm of 4 groups:

Group A (30 patients, 25%) without evidence of DN and absent IR with an average HbA1c of 8.5% - (Fig.6).

Group B (42 patients, 35%) with mild DN and mild IR (average 52%) and average HbA1c of 8.7% - (Fig.7).

Group C (30 patients, 25%) with moderate DN and moderate IR (average 70%) and average HbA1c of 7.9% - (Fig.8).

Group D (18 patients, 15%) with severe DN and severe IR (average88%) and average HbA1c of 8.2% - (Fig.9).

These results were strongly statistically significant (P<0.001) concerning the positive correlation between IR & DN irrespective of HbA1c level as a glycemic marker.

The laboratory parameters were supporting the results as well. The triglyceride levels were higher in group D & C patients with highest IR levels compared to the other 2 groups and matching the results of the Ezscan.

The CRP & IL-6 results were higher in group D & C patients reflecting the degree of inflammation & DN and matching the results of the Sudoscan.

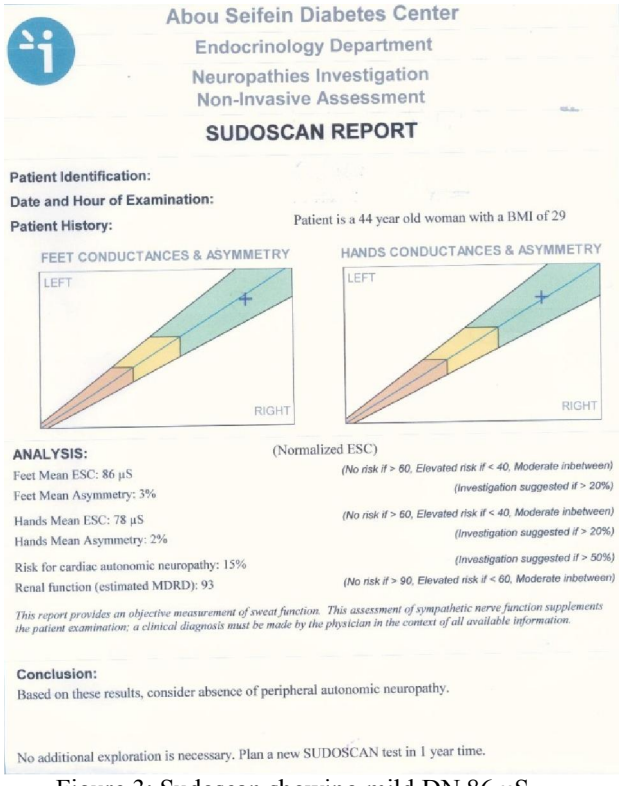
Abou Seifein Diabetes Center
Endocrinology Department
Neuropathies Investigation
Non-Invasive Assessment
SUDOSCAN REPORT
Patient Identification:
Date and Hour of Examination:
Patient History: Patient is a 44 year old woman with a BMI of 29
FEET CONDUCTANCES & ASYMMETRY
HANDS CONDUCTANCES & ASYMMETRY
LEFT
RIGHT
ANALYSIS: (Normalized ESC)
Feet Mean ESC: 86 µS (No risk if > 60, Elevated risk if < 40, Moderate inbetween)
Feet Mean Asymmetry: 3% (Investigation suggested if > 20%)
Hands Mean ESC: 78 µS (No risk if > 60, Elevated risk if < 40, Moderate inbetween)
Hands Mean Asymmetry: 2% (Investigation suggested if > 20%)
Risk for cardiac autonomic neuropathy: 15% (Investigation suggested if > 50%)
Renal function (estimated MDRD): 93 (No risk if > 90, Elevated risk if < 60, Moderate inbetween)
This report provides an objective measurement of sweat function. This assessment of sympathetic nerve function supplements the patient examination; a clinical diagnosis must be made by the physician in the context of all available information.
Conclusion:
Based on these results, consider absence of peripheral autonomic neuropathy.
No additional exploration is necessary. Plan a new SUDOSCAN test in 1 year time.

Figure 3: Sudoscan showing mild DN 86 µS

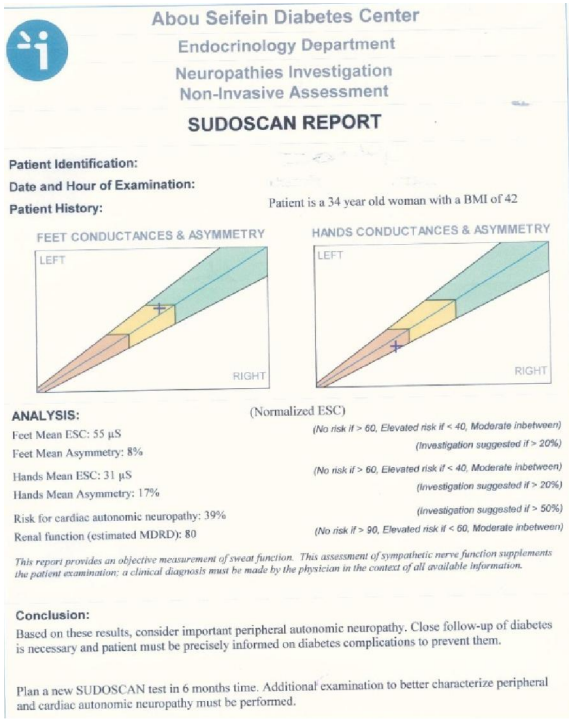
Abou Seifein Diabetes Center
Endocrinology Department
Neuropathies Investigation
Non-Invasive Assessment
SUDOSCAN REPORT
Patient Identification:
Date and Hour of Examination:
Patient History: Patient is a 34 year old woman with a BMI of 42
FEET CONDUCTANCES & ASYMMETRY
HANDS CONDUCTANCES & ASYMMETRY
LEFT
RIGHT
ANALYSIS: (Normalized ESC)
Feet Mean ESC: 55 µS (No risk if > 60, Elevated risk if < 40, Moderate inbetween)
Feet Mean Asymmetry: 8% (Investigation suggested if > 20%)
Hands Mean ESC: 31 µS (No risk if > 60, Elevated risk if < 40, Moderate inbetween)
Hands Mean Asymmetry: 17% (Investigation suggested if > 20%)
Risk for cardiac autonomic neuropathy: 39% (Investigation suggested if > 50%)
Renal function (estimated MDRD): 80 (No risk if > 90, Elevated risk if < 60, Moderate inbetween)
This report provides an objective measurement of sweat function. This assessment of sympathetic nerve function supplements the patient examination; a clinical diagnosis must be made by the physician in the context of all available information.
Conclusion:
Based on these results, consider important peripheral autonomic neuropathy. Close follow-up of diabetes is necessary and patient must be precisely informed on diabetes complications to prevent them.
Plan a new SUDOSCAN test in 6 months time. Additional examination to better characterize peripheral and cardiac autonomic neuropathy must be performed.

Figure 4: Sudoscan showing moderate DN 55 µS

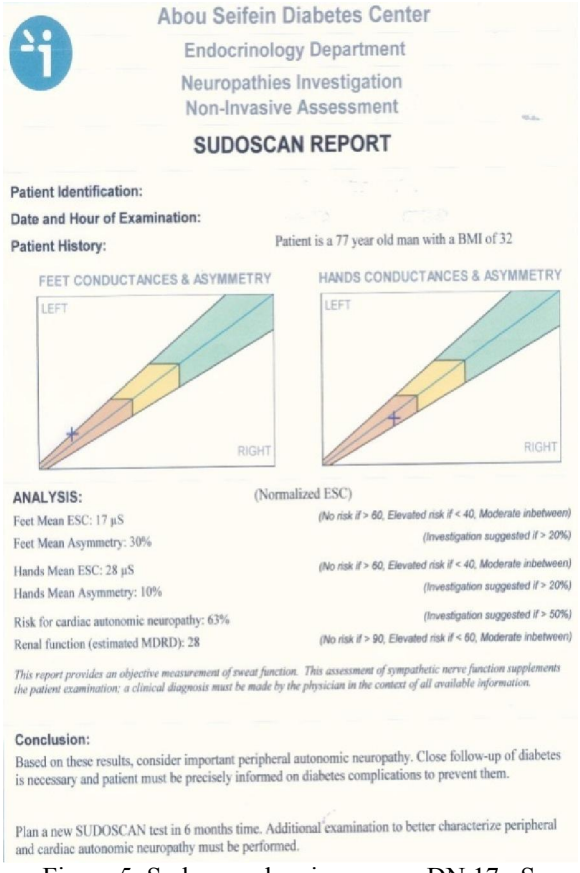
Abou Seifein Diabetes Center
Endocrinology Department
Neuropathies Investigation
Non-Invasive Assessment
SUDOSCAN REPORT
Patient Identification:
Date and Hour of Examination:
Patient History: Patient is a 77 year old man with a BMI of 32
FEET CONDUCTANCES & ASYMMETRY
HANDS CONDUCTANCES & ASYMMETRY
LEFT
RIGHT
ANALYSIS: (Normalized ESC)
Feet Mean ESC: 17 µS (No risk if > 60, Elevated risk if < 40, Moderate inbetween)
Feet Mean Asymmetry: 30% (Investigation suggested if > 20%)
Hands Mean ESC: 28 µS (No risk if > 60, Elevated risk if < 40, Moderate inbetween)
Hands Mean Asymmetry: 10% (Investigation suggested if > 20%)
Risk for cardiac autonomic neuropathy: 63% (Investigation suggested if > 50%)
Renal function (estimated MDRD): 28 (No risk if > 90, Elevated risk if < 60, Moderate inbetween)
This report provides an objective measurement of sweat function. This assessment of sympathetic nerve function supplements the patient examination; a clinical diagnosis must be made by the physician in the context of all available information.
Conclusion:
Based on these results, consider important peripheral autonomic neuropathy. Close follow-up of diabetes is necessary and patient must be precisely informed on diabetes complications to prevent them.
Plan a new SUDOSCAN test in 6 months time. Additional examination to better characterize peripheral and cardiac autonomic neuropathy must be performed.

Figure 5: Sudoscan showing severe DN 17 µS

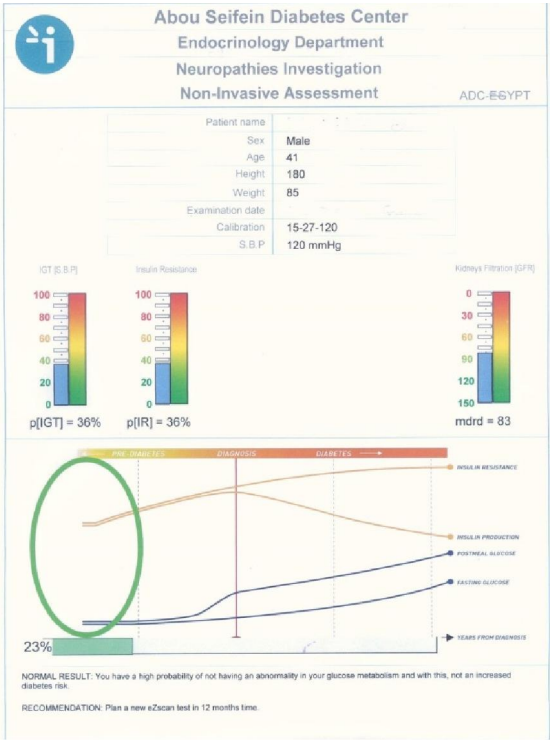

Figure 6: Ezscan group A showing no IR 36 %.

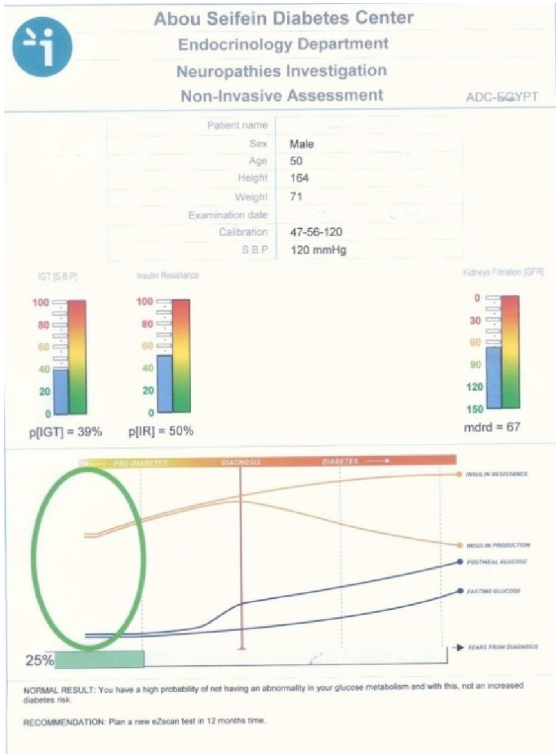

Figure 7: Ezscan group B showing mild IR 50 %.

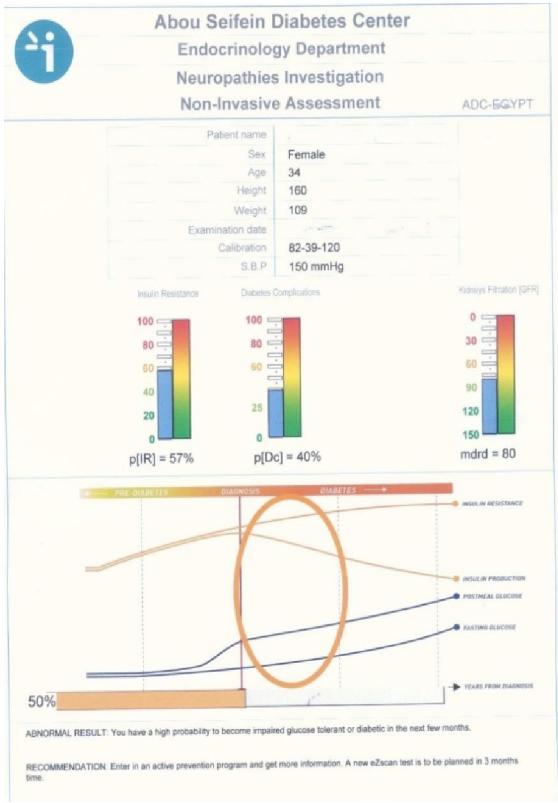

Figure 8: Ezscan group C showing moderate IR 57 %

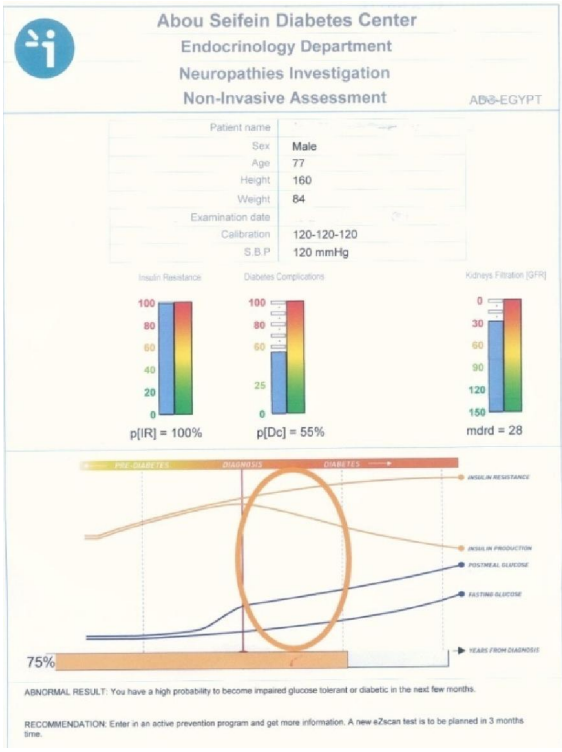

Figure 9: Ezscan group D showing severe IR 100 %

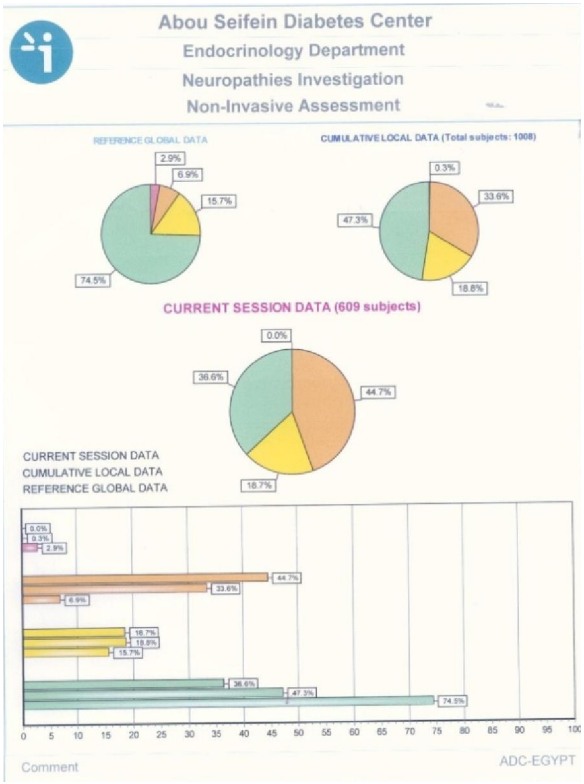

Figure 10: Cumulative Data

MDRD & eGFR were correlating with the degree of IR & DN, where lowest results were found in group D & C.

A weaker positive correlation could be detected between the level of glycemia (HbA1c) and DN. A finding supporting our clinical observation and the primary outcome of our study and confirming that dysglycemia is not the only leading cause for DN in our tested population, but rather IR is a more sensitive correlating feature and a major causative factor in the development of this micro-vascular complication.

Among our included 120 patients, 60 cases were randomly selected (15 from each group) to be tested for both C-Reactive Protein (CRP hs) & Interleukin-6 (IL-6) as reliable inflammatory markers.(20).

Concerning the IL-6, this assay employs the quantitative sandwich enzyme-immunoassay technique (Quantikine ELISA) where normal IL-6 levels ranged between 0.01 – 11.5 pg/ml. (21). Our results were showing a 3-4 fold increase in both group D & C and 1-2 fold increase in both group A & B. These results were strongly correlating with the severity of IR & the degree of DN, (P<0.005).

While concerning the CRP, this test done by Immuno Turbidimetric assay with a normal range of less than 3 mg/dl. (22). The results were also matching with the results of the IL-6 assay but with a weaker positive correlation to IR & DN (P,0.05) a finding that could be related to the fact that CRP is a more labile inflammatory marker than the IL-6 and could be elevated in many acute inflammatory conditions, however the big difference in cost between the IL-6 & the CRP tests is in favor of the last.

4. Statistics

Statistics data are shown in Tables 1 and 2.

Table (1) IR & DN

Source of variation	Sum of squares	Degree of freedom	Estimated v	F
Due to X1 residual	4.758 0.0005625	1 118	4.758 0.000047	995122.7
Total	4.75856	119		
P < 0.001 (R2 99%)	Subtotal F at 0.001level of significance = 3.4		R2 =0.99=99%	

Rx1, y = -0.99 reflecting a highly significant correlation between IR & DN.

Table (2) HbA1c & DN

		d.f.		
Due to X1	2.6728	1	2.6728	151.21
Residual	2.0857	118	0.017676	
Total	4.7585			
P<0.001– R2 56%				

Rx2, y =+0.75 reflecting a mild to moderate correlation between HbA1c & DN.

5. Discussion

Insulin resistance is a complex metabolic disorder that challenges a solitary explanation by a single etiological pathway. Accumulation of various lipid metabolites and altered immune pathways, all have been implicated in the pathogenesis of insulin

resistance. However, these pathways are also closely linked to changes in fatty acid uptake, lipogenesis, and energy expenditure that can affect ectopic lipid deposition.(16,19)

Ultimately, these cellular changes may congregate to promote the accumulation of lipid metabolites in the liver and skeletal muscles, a common final pathway leading to impaired insulin signaling and eventually insulin resistance. (12)

In clinical practice, it is difficult to diagnose insulin resistance syndrome by a single laboratory test. (11, 16). Diagnosis is based on clinical findings and laboratory tests and is usually based on the presence of comorbid conditions.(13,14)

In our study, IR once more is further unmasked, the pathophysiological alterations of this metabolic derangement is confirmed.

The results are in favor of the role of IR in the pathogenesis of DN which is not only related to the hyperglycemic burden (HbA1c) but rather to the biochemical alterations that accompany IR at the cellular level; (17)this time the victim is the Nervous System.

Glucose is not the only disturbed metabolite in the course of diabetes, fatty acids & amino acids are involved as well in this altered milieu (12). Maybe because hyperglycemia is a famous and easily measured molecule in clinical practice in comparison to other parameters, this fact gave him the leadership but definitely the pathogenesis of diabetes complications is more complex and other players are involved.

Our study confirms previous trials as in the Diabetes Control & Complications Trial (DCCT) where higher insulin resistance at baseline - estimated by Glucose Disposable Rate - was associated with increased subsequent risk of both micro- and macro vascular complications (diabetic retinopathy).(10)

HbA1c level - as a reflection of the hyperglycemic burden - was almost the same in the 4 groups despite the big differences in the severity of DN & IR levels in the 4 groups.

In our practice if we have relied only on symptoms or solely onthe clinical diagnosis of DN we would have missed many patients suffering from silent progressive DNwith or without autonomic involvement.

Interleukin-6 (IL-6) acts as both a pro-inflammatory cytokine, and anti-inflammatory myokine. It is encoded by the IL-6 gene and is significantly elevated with exercise, during infection and after trauma especially with tissue damage. Many chronic conditions are associated with high levels of IL-6 including type 2 diabetes. (23).From this prospective, we included IL-6 & CRP as major inflammatory markers that reinforce our hypothesis of IR as a chronic inflammatory condition that is directly predisposing to DN.

From our cumulative data of 1008 cases (Fig.10) that performed Ezscan & Sudoscan at our center, we concluded that this medical software (by Impeto) is a very useful non-invasive and accurate diagnostic tool for the early diagnosis of Insulin Resistance & Diabetic Peripheral & Autonomic Neuropathy. The basic pathophysiology behind this technology is supported by the growing number of clinical studies worldwide which show a strong association between small nerve neuropathies, IR and DN.

It helps the health care providers to focus on IR - along with hyperglycemia - as a primary pathological entity, not to mention the importance of the early diagnosis of IR when dealing with other comorbid conditions such as fatty liver, obesity and above all the cardio-metabolic risk continuum.(13)(18)

6. Conclusion

DN is a common incident in diabetic patients, it occurs earlier than we expect in the process of the disease. In our clinical practice IR plays a role in type 1 DM requiring higher than expected insulin doses, further study is required to confirm this finding (19).

Our study confirms the strong correlation between IR& DN in type 2 diabetic patients irrespective of the glycemic level. It also confirms the accuracy and simplicity of both the Ezscan & Sudoscan as a non-invasive diagnostic tool for IR & DN respectively.

These findings should be considered by the health care professionals dealing with Diabetes and its complications to follow an early and more aggressive therapeutic approach with their patients for better clinical outcomes.

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4/24/2015